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International Medical Digest

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General Medicine

Tetraethylammonium Chloride in the Treatment of Angina Pectoris — ATKINSON, WILLIAM J., JR.—*American Heart Journal*, 39: 336 (March) 1950.

In January, 1947, the writer first began the treatment of a patient who had unusually severe and intractable angina pectoris with tetraethylammonium chloride (TEAC). Symptomatic improvement was striking and he was encouraged to treat other patients. "Twenty-eight patients suffering from angina pectoris have now been treated with tetraethylammonium chloride; 18 have been on this therapy for from 6 to 20 months."

Patients were evaluated by the number of attacks of anginal pain per week and by exercise tolerance in terms of everyday tasks. "Exercise tolerance was recorded in terms of the number of successive blocks walked without stopping before a pain was induced, and the number of stairsteps climbed. Although this method is subject to variations caused by many factors, it permits clinically adequate assessment of general trends in the patient's condition over a period of time."

"The optimal dose of tetraethylammonium chloride for treatment of angina pectoris varied greatly from patient to patient. Responsiveness to the drug was usually increased by severe heart disease, old age, arteriosclerosis, and some forms of hypertension. If the dose was too large, patients with one or more of these factors were more likely to experience greater hypotension and other unpleasant side effects. The optimal dose was determined for each patient by beginning with small intravenous doses (50 or 100 mg.) and working up to the optimal dose.

"The patient is told at the time of administration that he may experience a transitory slight metallic taste, followed by a tingling or cold sensation in hands and feet. He is then asked to tell when each of these occurs and the strength of the sensation. Blood pressure readings are taken at two and five minutes. If he does not develop tingling, or if it develops in his hands and not his feet, the dose is probably too small and should be increased, provided the blood pressure has not fallen too precipitously. (Moderate falls in blood pressure are well tolerated and the fall is very temporary.) If a larger dose is necessary, it can usually be given 10 or 15 minutes after the first dose. The smallest dose which will give a pronounced tingling sensation in the feet seems to be the optimal dose.

"Tetraethylammonium chloride is never given except with the patient lying down. When the optimal dose is found, blood pressure is taken every five minutes after the injection until it has risen to normal range. This is judged as the amount of time that a patient should remain in the supine position after treatment, and gives a rough estimate for the time that he must remain recumbent after future treatments. After this period has elapsed, the patient is allowed to sit up, and, if he is not dizzy, he may stand up. If he feels dizzy, he should lie down for another 15 minutes and then try again." Using these precautions, the writer has encountered only a few minor unpleasant side reactions, and no serious reactions, and no toxicity. Early in the series, he had 1 instance of momentary syncope in a 71 year old man who stood up too soon.

"When doses were too large, several patients became slightly nauseated, either immediately, or on the way home. Several experienced dizziness and lightheadedness for periods up to 12 hours after treatment. These reactions probably represented postural hypotension. Further treatment with smaller doses did not produce unpleasant effects.

Table I. Average Response to TEAC as Classified by Age

Age	Average Number of Pains Per Week		Average Number of Blocks Walked		Average Number of Stairsteps Climbed	
	Before Treatment	During Treatment	Before Treatment	During Treatment	Before Treatment	During Treatment
30-40 years 1 patient	35	1	0	2	0	20
40-50 years 1 patient	Steady ache	0–1	Good increase in exercise tolerance, but blocks and stairs not measured			
50-60 years 8 patients	16	2	1 caused pain	5 caused pain	15 caused pain	25 did not cause pain
60-70 years 10 patients	28	4	2 caused pain	6 caused pain	11 caused pain	20 did not cause pain
70-80 years 6 patients	12	3	6 caused pain	12 did not cause pain	13 caused pain	27 did not cause pain
80 plus 2 patients	3	2	3 caused pain	6 caused pain		

"When an inadequate dose was given, using sensory stimuli as an indicator, the patient often did not get as good symptomatic improvement of angina as on subsequent occasions when he received a larger dose.

"Once the patient's dose and the length of time during which he will have to lie down afterward are determined, treatment may be administered on subsequent visits without the repeated blood pressure determinations, provided the patient has had no major change in cardiac status. Occasionally a patient will fail to get a full sensory stimulus from a previously effective dose, and it will be necessary to repeat the dose with an increase of 50 mg. On the other hand, it may be found that, after several treatments, the dose can be decreased slightly without loss in effectiveness."

"Frequency of treatments was governed by the duration of symptomatic relief and practicability. In general, therapy was given about once every one or two weeks. For the most severe angina pectoris, it was given twice a week until the patient improved sufficiently to decrease the frequency of visits. Occasionally during very severe periods, patients were hospitalized and treatment given every one or two days. Some patients who were on weekly treatments noted a return of pain after three or four days and it was considered that treatment twice a week would be more beneficial, but it was usually impractical for them to be seen that often."

"The length of time these 28 patients were treated with tetraethylammonium chloride was : 18 to 20 months, 2 patients; 15 to 18 months, 1; 12 to 15 months, 3; 9 to 12 months, 6; 6 to 9 months, 6; 3 to 6 months, 6; and 1 to 3 months, 4 patients. This does not include the control period for evaluation which preceded the special therapy for each patient. Most patients had very severe heart disease with unmistakable clinical and electrocardiographic evidence of marked coronary insufficiency. Over 70 per cent had been either decompensated at sometime or had a myocardial infarction previous to this study." All but 2 were over 50 years of age and 65 per cent were over 60 (table I).

"In this series 25 of the 28 patients showed definite improvement during treatment. In some, this was noted immediately, whereas others did not show improvement until they had been treated twice a week for several weeks. Of those who improved, 65 per cent showed a significant decrease in anginal pains, and 60 per cent showed a noticeable increase in exercise tolerance.

"Most of the classifications, as arranged according to apparent severity of the disease, showed similar results, except for the group with previous infarction and the group with previous infarction and pre-

vious decompensation. Those composing these groups showed, in general, a poorer response than the others. However, no apparent harmful effects were seen with many doses of tetraethylammonium chloride in these patients with very severe heart disease.

"There was not much difference in the response of the various age groups. Two patients over 80 years of age were treated without apparent harmful effects. Response of the other older age groups was surprising and brings up many interesting questions as to the possible mechanisms of action of tetraethylammonium chloride in these patients.

"One interesting result was relief of persistent substernal, epigastric, and precordial burning, 'hurting,' and aching pains and soreness which had not been previously relieved by many nitroglycerin tablets. This was noted in 8 patients with angina in whom continuous pain had been present from a few hours up to several weeks. Two other patients, who, after an acute infarction, had almost steady aching and soreness for three and four months, respectively, were relieved, though they continued to have some angina of effort. These pains, like the pain in an acute anginal attack, were relieved within two to five minutes after intravenous administration of tetraethylammonium chloride. Nine of these 10 patients had definite signs of coronary insufficiency, and 5 of them had had previous infarctions. . . . Intravenous calcium gluconate or nicotinic acid in doses sufficient to give a definite sensation, administered before tetraethylammonium chloride in 5 of the 10 patients, gave relief in only 1.

"Of 10 patients whose electrocardiograms were followed carefully for nine months or more, 7 showed no change, 2 showed T wave improvement (1 of these returned to normal), and 1 became worse."

In 4 patients in whom a significant electrocardiographic change has been obtained during an anginal attack, the tracing has reverted to its original appearance two to four minutes after the administration of tetraethylammonium chloride and maintained this configuration. "One of these patients had been having continuous pain for three days, and had taken 30 glyceryl trinitrate tablets without relief. The other 3 patients had their pain for only short periods of time."

The blood pressure and pulse changes were usually not very great, but patients must remain recumbent until they no longer have postural hypotension.

"Since tetraethylammonium chloride gives a marked sensory stimulus, and since many anginal patients have a psychic makeup rendering them highly responsive to suggestion, it was thought that this factor should be evaluated.

"Eleven of the 25 patients who had shown improvement on tetraethylammonium chloride were given placebos of intravenous calcium gluconate or, if they were on digitalis, nicotinic acid in sufficient doses to give a good sensory stimulus. This was continued for 5 to 11 weeks. Neither of these is a completely inert placebo. Calcium gluconate has been advocated by some in the treatment of angina, and nicotinic acid has vasodilator effects which may be of benefit." However, they seemed to be the best substances available which would give a somewhat similar sensory stimulus, and they have no known harmful effects in these patients. "Four patients who had responded to tetraethylammonium chloride were no better on placebos than before either treatment. Six were better on tetraethylammonium chloride than on the placebo, but were better on the placebo than without either. One showed as much response to the placebo as to tetraethylammonium chloride.

"This suggests that, although psychic stimulus does play a part in some patients (65 per cent of the small number tried), it probably was not the only factor responsible for improvement in the majority of those who responded to the drug (only 10 per cent did as well on placebos as on tetraethylammonium chloride).

"Four of the patients in this series have died. In 2, death occurred after the patients had been on placebos for five and seven weeks, respectively." In the other 2, death occurred two and five weeks after their last treatments with tetraethylammonium chloride and was not, as far as could be determined, due to any ill effects of the drug.

"In this small series, no conclusions can be drawn as to beneficial results other

than symptomatic improvement. However, especially in patients for whom all other methods of treatment have proved to be inadequate, the additional relief obtained with tetraethylammonium chloride can be most gratifying."

A Low Sodium Diet for Hypertensive Vascular Disease Precipitating Addison's Disease and Miliary Tuberculosis. Report of a Case—FRIEDENBERG, SIDNEY — *New England Journal of Medicine*, 242: 277 (February 23) 1950.

"The treatment of hypertensive cardiovascular disease or congestive heart failure with a low sodium diet is no longer considered an innocuous procedure. . . . Grave complications and death may ensue from sodium depletion.

"The low sodium syndrome is strikingly similar to acute adrenocortical deficiency. The clinical picture may develop with severe restriction of dietary salt, the use of mercurial diuretics that inhibit tubular reabsorption of sodium and intrinsic renal disease, such as tuberculosis of the kidneys or, rarely, chronic glomerulonephritis."

Another complication of a low sodium diet is the flare-up of quiescent miliary tuberculosis. "In the following case Addison's disease (chronic adrenocortical deficiency) and miliary tuberculosis were precipitated by a low sodium diet for hypertensive cardiovascular disease."

"C. B., a 63 year old housewife, was in good health during February, 1948, except for occipital headaches and subjective vertigo, for which she had been receiving treatment intermittently since 1944. During these years her blood pressure varied from 222/120 to 160/108. Medication had consisted of phenobarbital and the vasodilator group of drugs. In March a blood pressure of 220/110 was found. She was placed on a low sodium (400 mg.) diet and reported complete relief of her symptoms several weeks later. Her blood pressure then was 140/90. From this point on she consulted numerous physicians, at varying intervals.

"In April she believed that she was losing ground; she was weak and had lost considerable weight, the exact amount not being known. In June she became anoretic and there were days when she felt nauseated but she remained on the low sodium diet. In August she noticed darkening of her skin. On August 15 she began to vomit and refuse food. She was admitted to the hospital on September 4.

"The patient was acutely ill. Although conscious and apparently aware of her surroundings her lassitude was so marked that she did not utter a sound. With no history accompanying her, the diagnosis was made on physical examination alone.

"There was a bluish bronze pigmentation of the face; the lips were cyanotic, and the respirations rapid. The pulse was not palpable, the heart sounds were inaudible, and the blood presssure was unobtainable. There was a distinct patch of bronze pigmentation on the buccal mucosa. The liver and spleen were not palpable. There was no peripheral edema.

"Intravenous administration of saline solution was begun immediately, the presumptive diagnosis being an Addisonian crisis. Aqueous adrenocortical extract was given intravenously through the infusion tubing, and 5 mg. of desoxycorticosterone acetate was given intramuscularly. An hour later the patient had sufficient strength to speak in a whisper.

"The same therapy was continued, the patient improving each day. By September 13 she was eating a large tray of food, taking salt tablets by mouth, and receiving 3 cc. of Lipo-Adrenal Cortex extract intramuscularly daily.

"Fever was noted on her second hospital day, the temperature ranging from 99 to 104° F. Although tuberculosis was suspected, it could not be proved. Penicillin therapy was ineffective. A roentgenogram of the chest taken with a portable machine was normal. Anaerobic blood cultures were reported negative. No guinea pigs were available for inoculation. Acid-fast stains of the urinary sediment were negative. The eyegrounds were inspected for miliary tubercles but none were found, the eyegrounds being considered normal. The sedimentation rate was elevated, 32 mm. in one hour, the normal range being 15 mm. or less.

"Examination of the chest on September 24 revealed dulness to percussion at the bases. Another roentgenogram on the next day confirmed the findings, the film being interpreted as 'suggestive of miliary tuberculosis.'

"Administration of streptomycin hydrochloride, 250 mg. every six hours, was begun on September 25, and by September 28 the temperature range was not above 99° F., remaining so for the rest of her hospital stay.

"The patient gained weight, and her color improved. It was difficult to persuade her to remain until a minimal course of streptomycin could be given.

"On September 7 the specific gravity was 1.026, with negative tests for sugar and acetone and a + test for albumin, and the sediment contained heavy amorphous urates; three days later the specific gravity was 1.012, with negative tests for sugar and acetone and a + test for albumin, the sediment containing 5 to 10 white blood cells per high power field. Stains for acid-fast bacilli were negative. Blood cultures taken on September 21 and October 8 and 23 were reported negative after three weeks. On September 22 agglutination tests for typhoid, paratyphoid, Proteus ox19 and *Brucella abortus* were negative in all dilutions. A glucose tolerance test showed a fasting blood sugar of 80 mg. per 100 cc. initially, 100 mg. after one-half hour, 106 mg. after two hours and 136 mg. after three hours."

"A roentgenogram of the chest on October 18 showed no change from the previous film. The sedimentation rate on October 23 was 22 mm. in one hour, a distinct improvement. The blood pressure was 136/80 and remained at that level during the rest of her stay.

"The patient was discharged on October 26. The total dosage of streptomycin was 30 Gm. given in 30 days. A relative of the patient was instructed to inject 1 cc. of Lipo-Adrenal Cortex extract daily.

"The patient was readmitted to the women's medical ward on February 2, 1949. She had remained well for several months, but a combination of circumstances, both emotional and economic, had led to neglect of diet and irregular injections of adrenocortical extract. She became weak and complained of nausea. One week before admission she complained of pain in the right loin.

"On admission the patient was disoriented, dyspneic and incontinent. A roentgenogram taken with a portable machine was reported as showing a heart enlarged in all diameters. The right leaf of the diaphragm was elevated, and an area of increased density at the right base suggested a localized pneumonitis. Some generalized coarse mottling of the lungs was noted.

"Many examinations of the urine were negative except for a trace of albumin. The specific gravity ranged from 1.006 to 1.020. Blood chemical and hematologic values were similar to those observed on the first admission.

"The patient gradually improved under the same therapeutic regime followed during her first admission. In addition, because of heart failure precipitated by the toxemia and pneumonitis, she was digitalized (February 5). Two small blood transfusions of 250 cc. each were given to combat the prostration and anemia. By February 7 she was able to take fluids and salt by mouth.

"It was believed at this time that her maintenance requirement of desoxycorticosterone acetate should be estimated and, when she was strong enough, a pellet implanted.

"Streptomycin was discontinued on February 14 because of complaints of dizziness. There had been no fever on this admission so that temporary interruption of the streptomycin course was considered fairly safe.

"The patient's progress continued. She looked forward to returning home. On February 25 she vomited once. Despite the fact that laboratory studies were within normal range she appeared weaker. Adrenocortical extract was substituted for the desoxycorticosterone acetate on February 28.

"The patient died suddenly on March 2.

"At postmortem examination a pale, sallow, yellowish discoloration of the skin resembling that seen in Addison's disease was observed. There was no marked discoloration of the mucous membrane surfaces except in focal areas. The extremities were otherwise not remarkable. A healed wound was present over the right internal malleolus—the result of a previous attempt at intravenous injections of fluid. There was external evidence of edema.

"When the pleural cavity was opened the left hemithorax contained some dense fibrous adhesions, some of which could

easily be broken. Within the left pleural cavity there was approximately 800 cc. of a yellow serous fluid. The right pleural cavity also contained many dense adhesions, which could be broken with difficulty, and 150 cc. of the same type of yellowish fluid. The lungs appeared normal in shape but were firmer in consistence than usual. The right lung weighed 270 Gm., and the left 430 Gm. On section the left lung exuded a bloody, frothy serous fluid. The pleural surface of the right lung was covered by dense fibrous tissue, which was somewhat edematous. Numerous small miliary grayish white areas measuring 4 to 6 mm. in diameter were seen throughout the cut surface of the right lung.

"The heart weighed 410 Gm. The pericardial cavity and the pericardium proper were not remarkable. Examination of the coronary vessels showed moderate sclerosis but no evidence of any occlusion. The auricular and ventricular cavities were not remarkable. Examination of the valves, endocardium and myocardium showed no significant pathologic changes.

"The liver weighed 1,730 Gm. and had a mottled appearance. Beneath Glisson's capsule there were numerous small, pinpoint miliary foci. On section they resembled the lesions seen in tuberculous infections. The intervening hepatic tissues appeared somewhat congested.

"Examination of the gastrointestinal tract showed no significant pathologic changes except for marked edema of the subperitoneal tissues, especially those on the abdominal wall and within the mesentery proper.

"Throughout the cortical surface of the spleen there were numerous grayish white streaks, which on cut section appeared well defined. There was also marked hyperplasia of the malpighian bodies, with associated congestion of the sinuses. The spleen weighed 300 Gm.

"No significant gross pathologic changes were observed in the lymph nodes examined.

"The perirenal tissues were somewhat edematous, but the kidneys were normal in position; the right kidney weighed 150 Gm., and the left 200 Gm. The capsule stripped with ease, leaving a mottled, pinkish gray surface studded with numerous miliary tubercles. On cut section the corticomedullary junctions were quite distinct and yellowish red. The arcuate vessels were quite prominent; the ureters and bladder showed no significant pathologic changes.

"Examination of the reproductive system revealed the uterus, tubes and ovaries to be somewhat atrophic, without any significant gross pathologic changes.

"The periadrenal regions showed marked edema with marked invasion of the cortex and medulla by numerous grayish white tubercles. The intervening tissue was pink, and a somewhat yellowish viscid fluid exuded from the cut surfaces.

"No significant gross changes were observed in the pancreas.

"Permission was not given to open the head.

"Microscopical examination revealed moderate sclerosis of the coronary vessels. Otherwise the heart muscle tissue was not remarkable. There was marked serous exudation into the pulmonary alveoli, with numerous miliary tubercles throughout. There was no infiltration of the blood vessel walls or any evidence of a pneumonic process.

"Many miliary tubercles were seen in numerous zones of the hepatic lobules. The corticomedullary areas showed marked thickening of the smaller arterioles, with narrowing of some of their lumens.

"No active inflammatory process was present, although occasional tubercles were found throughout the kidney parenchyma proper.

"The normal adrenal architecture had been completely distorted by a diffuse tuberculous involvement. There were occasional deposits of pink-staining hyaline material resembling amyloid. Throughout the rest of the adrenal gland there was a moderately diffuse lymphocytic infiltration.

"The splenic pulp showed numerous tubercles of the miliary type.

"No significant microscopical changes were observed in the pancreas.

"The final pathological diagnoses were miliary tuberculosis affecting all organs except the pancreas, possible amyloid deposits in the adrenal glands, chronic passive congestion of the liver, lungs and spleen and bilateral, moderate hydrothorax. Death was due to a combination of adrenal insufficiency and toxemia associated with miliary tuberculosis."

The Brucella Ring Test in Mixed Raw Milk Supplies — BREMER, HARRY E. — *American Journal of Public Health*, 40: 290 (March) 1950.

"Ten years ago in July, the milk control work in the state of Vermont was transferred from the local town health officers in the 246 towns of the state to the Vermont Department of Agriculture. The latter department is also the control agency, in cooperation with the United States Bureau of Animal Industry, which conducts the Brucellosis Eradication Program. Supervision of state milk inspection and brucellosis eradication are therefore centered in the same state department."

The problem is to reduce the infection that may be present in the 6 per cent of the retail raw milk supply which is sold to the public. "The blood test is the official test used for brucellosis eradication work in livestock. The early results of this test showed that two thirds of the herds that had been tested were infected with brucellosis and that 17 per cent of the animals tested were reactors. About one fourth of the retail milk supply at that time was pasteurized and the number of cases of undulant fever reported by the State Health Department was steadily increasing each year."

"It was apparent that universal pasteurization could not be enforced. Public sentiment did not favor it and the daily milk sales by many dealers were so small that pasteurization was considered impractical. Consequently the milk serum agglutination test was adopted as a screen test to locate infected herds which supplied milk to retail raw milk distributors."

The Milk Serum Agglutination Test.—The writer began using this test in 1941 by testing 690 samples from herds which furnished the raw milk sold in the state. "It was found that 12 per cent of the herds showed infection." It was desirable to know which cows were infected in addition to knowing that there was infection in the herd. The individual quarters of all cows in the herds which showed infection were sampled separately. "In this work, separate quarter samples were tested from 1,853 cows in 92 herds, with the result that there were 15 per cent reactors and 6 per cent suspects on the milk serum test. These were the herds showing infection on the composite herd milk samples."

Owners of infected herds which contributed to the raw milk supply for public sale were given the option of blood testing their herds and eliminating reactors or of pasteurizing the milk which they sold.

"Forty of the 92 herds were then blood tested under the Cooperative State-Federal Plan. Of the 1,181 cows in these 40 herds, 22 per cent were reactors and 9 per cent suspects. Six of these herd owners discontinued selling milk in local markets, 6 other dealers started to pasteurize the milk which they sold, and the 28 remaining herd owners removed reactors and continued the sale of raw milk.

"Dealers and consumers became cooperative and, within a few short years, the percentage of pasteurized milk sold in the state rose from 24 per cent to 50 per cent, then to 66 per cent, and on July 1, 1949, to 94.2 per cent."

Some animals reacting to the official blood test would have been overlooked if one had used the milk serum test as the basis for the determination of reactors. Results indicated that blood serum gave a stronger reaction than milk serum. "In most cases of a slight reaction on the milk serum test, the blood test of that animal was suspicious or positive."

The Ring Test.—The writer began using the ring test a year ago to see if he could get the results that were being claimed for the test. All of the results are on milk, since very little cream is now being separated on the farms. A vast amount of laboratory work could be eliminated if the ring test of mixed herd milk could be substituted for the milk serum test on the milk from each quarter of all milking animals. "If that could be done, one ring test would take the place of 200 samples previously analyzed in a 50 cow herd. It is now recognized that it would have been better to have sampled each 40 quart can delivered by a producer separately in cases where the herds were larger than 20 cows." The herds studied varied in size up to 83 animals.

"Herd samples of mixed milk were taken for the ring test from all of the herds whose milk was delivered to several milk-receiving plants. Composite samples were taken from the producers' cans to avoid

vat contamination. A single sample therefore represented the mixed milk of herds varying in size up to 83 animals.

"Results of these ring tests indicated that where a positive or suspicious reaction occurred and was followed by a blood test of the herd, the blood test also disclosed positive or suspicious animals.

"Not all of the herds that showed positive or suspicious ring tests were blood tested, so that complete comparisons could not be made. The producer must sign up before the blood test is applied. There was an interval of 60 to 90 days from the time the ring tests were applied to the time of completion of the blood tests. This time interval between the two tests introduced another variable factor. A substantial number of dry cows had freshened during these two fall months and the official blood tests therefore included a number of cows that were dry when the ring tests were applied."

"In rural villages where the volume of milk sold is small and pasteurization of milk is not practical, these tests are of value in helping to improve the safety of the raw milk supply."

The Brucella Ring Test. Its Potential Value in the Control of Brucellosis— HAMILTON, ADDIE V. AND HARDY, ALBERT V. — *American Journal of Public Health*, 40: 321 (March) 1950.

The Brucella Ring Test is based on the fact that in whole milk the agglutinated organisms adhere to the fat globules and are carried to the surface as the cream rises. "A stained antigen is employed. In a positive test, the cream ring is colored by the agglutinated stained organisms. The milk below is white, or at most, slightly tinted. In the negative test, by contrast, the cream ring is uncolored while the milk is heavily colored. The test is simple to perform. One ml. of milk is placed in a test tube and 1 drop of stained antigen is added. This is mixed by a brief shaking. The test is incubated at 37° C. for 30 to 60 minutes and read.

"Antigen preparation is the initial and most important step in technique." Following comparative studies, the writers have used *Brucella abortus*, strain 19, Bureau of Animal Industry, for all antigen production. "The organisms were grown on potato infusion agar for 48 hours, were washed off with 0.5 per cent phenolized saline, then washed and collected by centrifugation. The bacteria were stained in a 1:5 dilution of Delafield's hematoxylin for five minutes. Best results were obtained on mixing 10 ml. of packed bacterial cells in 1,200 ml. of stain. The organisms were collected by centrifugation and the excess stain removed by repeated washing in acidified tap water. The final antigen is a suspension of stained *Br. abortus*, 4 per cent by volume, in a 50 per cent glycerin —50 per cent phenolized saline mixture.

"Variation in the sensitivity of different lots of antigen prepared from the same organism have been noted. A standardized antigen, prepared and distributed by an official agency, would aid greatly in the evaluation of this test.

"Ordinarily, the ring test is performed on undiluted whole milk. Agglutination titers may be obtained by diluting the sample in series using known negative whole milk as the diluent. . . . The ring test has been recommended chiefly for use in testing mixed milk samples." Data on individual animals will be more informative.

"Findings by the blood test, the whey test, and the ring test have been studied comparatively. . . . Present impressions are these: Cows strongly positive by blood test, are almost invariably also positive by ring test; conversely, those strongly positive by ring test are almost always positive by blood test. Any discrepancy in findings, with occasional exceptions, is in those animals which have weakly positive or doubtful reactions by one or the other test. The blood titer on an individual animal is ordinarily above the ring test titer, and commonly much higher. There is however, no regularity in the relationship. The two may show closely similar titers; on the other hand, the blood titer may be high while the ring test is positive only in undiluted milk. Since a positive ring test on an individual cow is often obtained only on undiluted milk, the limitations in value of a test on mixed milk samples is evident."

The whey agglutination is less sensitive than the ring test. "Specimens with weak positive reactions by ring test were often negative by whey agglutination.

"The ring test proved surprisingly reliable in identifying infected herds on examining a mixed sample from the herd. Presumably this is due in part to the fact that in this communicable disease, a considerable percentage of the animals in an infected herd are infected. In 67 of 68 herds studied, there was agreement between blood findings and ring tests performed on mixed milk samples. In 1 case, a weakly positive ring test was obtained on a herd presumed to be free of Bang's infection. Calfhood vaccination had been practiced, but ordinarily such animals have few or no agglutinins in serum or milk. This herd was not rebled to confirm the negative findings by serum agglutination.

"Conditions which might effect ring test readings have been studied. Results on the raw and the subsequently pasteurized milk were essentially identical. Shipped specimens with added preservative were satisfactory for testing. Tests on animals with mastitis were difficult to read and in obviously abnormal milk gave what appeared to be a false positive reaction. In animals, vaccinated as adults, agglutinins were present which made it difficult to interpret findings."

Ring tests on milk collected from individual cows, or on mixed samples from groups of cows, provide findings in close agreement with those obtained by serum agglutination tests. It has practical value.

"Raw milk is still used—and will continue to be consumed by rural families and in villages. Certainly every sample of milk from a supply for raw consumption which comes to a public health laboratory should be examined by a ring test." There should be a concerted effort to have the milk of all "family cows" on farms and in villages tested by ring test if a blood test has not been performed. "Using preservative, specimens can be collected in 1 ounce bottles—such as are used for fecal specimens—and mailed to the laboratory. The ring test is essentially an examination for the probable presence of a pathogenic organism in milk." If the early promise of this test is confirmed, it will be more nearly practicable to protect the public from the use of raw milk from Brucella infected cows.

"The second major value of the ring test will be in providing easy and frequent checks of clean herds. This will facilitate an early recognition of introduced infection. Thus, the problem of reestablishing control would be held at a minimum.

"In the absence of a general blood-testing program, the ring test will differentiate presumably clean from presumably infected herds. Limited facilities and resources for blood testing could be used where of greatest probable value.

"To what extent the ring test may be substituted for blood tests on individual cows can be determined only by extensive comparative studies. If the tests prove of nearly equal value, the one which uses specimens which are easy to collect will be utilized more readily and probably more frequently."

The ring test the writers view as an effective screening procedure. "The screen will be fine if samples come from individual cows, it will be very coarse if one sample of the mixed milk of a whole herd is tested, it will be a moderately effective screen if a sample from each can is collected. The ring test as a screen test will not replace the blood test; but it will minimize unproductive blood testing and will increase the importance of every blood test which is performed."

The writers recommend the ring test for trial and study, with emphasis on the latter. "No test procedure available is wholly reliable."

Observations on a Combined Colchicine and Roentgenotherapy of Leukemia — Keibl, Edwin and Lötsch, Anny —*Schweizerische medizinische Wochenschrift*, 80: 228 (March 4) 1950.

It has been demonstrated that colchicine, and to a lesser extent arsenic and trypaflavine, have a special effect on cell division. As particularly young cells, ready for division, showed an increase of mitoses after colchicine administration it was at first believed that this drug facilitates mitosis but one writer's work on tissue cultures showed that the drug actually has an inhibitory effect on the course of mitosis; microcinematographic pictures of tissue cultures showed that the mitoses start normally but are blocked during the first stage of the metaphase, and that an increased number of mitoses is found on tissue sec-

tions due to this blockage at a certain stage of division. The term of stathmokinesis was coined for this blockage at the stage of the metaphase and all substances which act on the course of mitosis in this manner were termed karyoclastic poisons. Such substances act particularly on young cells ready for division; that is, in the normal individual on the bone marrow erythroblasts and the cells of testicle and thyroid gland, and in cases of cancer on the cancer cells.

As early as 1908 a transitory leukopenia followed by leukocytosis was observed after colchicine, and later some authors found a reduction of the number of leukocytes in some cases of leukemia after colchicine administration; in addition in some acute cases a relative reduction of the myeloblasts was found.

In the majority of normal individuals the authors found after a single subcutaneous injection of 2 mg. of colchicine a leukopenia of short duration, followed by a leukocytosis of several hours' duration, while a few individuals showed only the leukocytosis; the differential count showed no marked modifications while the number of erythrocytes and hemoglobin concentration frequently showed a slight increase. No effect on the lymphatic cells was ever observed and the work was therefore confined to acute and chronic myeloid leukemias.

In most cases of myeloid leukemia the peripheral blood picture showed a reduction of the number of leukocytes, usually only of short duration; the differential picture showed no definite modifications. In the sternal marrow occasionally an increase of the mitoses of the erythroblasts was encountered, but strikingly no increase of the mitoses of the myeloid cells; however, in view of the difficulties of evaluation of mitoses in the sternal marrow these findings do not absolutely contradict some influence of the drug on the processes of cell division. Both in the bone marrow and in the peripheral blood morphologic modifications concerning nucleus and protoplasm were encountered after colchicine injections; a definite increase of the chromatin agglutination involved not only the nuclei of the mature cells but also those of the myelocytes, and some cases showed hyperchromatosis of the nuclear wall while vacuolization of nuclei and protoplasm was observed only rarely. The effect on the protoplasm frequently consisted in an increase of the toxic granulations and in the myeloblasts in an increase of the protoplasmatic detachments. The fact that this effect was not observed in normal bone marrow indicates that the drug acts selectively on cells ready for division and therefore has a potentiated act on the young cells of leukemia. Thus colchicine seems to influence the course of mitosis in myeloses and to have a toxic effect on nucleus and protoplasm.

It could be demonstrated on cutaneous metastases of a gastric cancer that a metastasis pretreated locally with colchicine and subsequently subjected to roentgenotherapy regressed completely and could not be demonstrated any longer on histologic examination while another metastasis which was subjected only to roentgenotherapy still showed all signs of active cancer tissue.

On the basis of this observation the authors tried combined colchicine and roentgenotherapy in leukemias. Before each session of roentgenotherapy a subcutaneous injection of 2 mg. of colchicine was given and the beginning of the numerical and morphologic modifications was determined by examinations of the peripheral blood picture at intervals of half an hour; the most appropriate time for the roentgenotherapy was found to be two hours after the injection in most cases. In all irradiations of the spleen a dose of 150 r was used, with a filter of 0.5 and a focal distance of 30 cm.

The first case concerned a man aged 47, with chronic myeloid leukemia of one year's standing. The symptoms were mainly those of progressive anemia and of a splenic tumor which extended into the lesser pelvis. The patient also suffered from intense kyphoscoliosis and from paresis of both legs since childhood caused by poliomyelitis. He had undergone removal of his left kidney at the age of 43 because of pyonephrosis and nephrolithiasis, thus the general condition did not seem favorable for successful treatment. The leukocytes numbered 160,000 on admission and were reduced to approximately normal values after six colchicine injections and irradiations; the differential count before treatment

showed 2 per cent myeloblasts, 6 per cent promyelocytes, 13.7 per cent myelocytes, 25.9 per cent metamyelocytes, 27 per cent staff cells, 19.7 per cent polymorphonuclear cells and 5.7 per cent lymphocytes, while after treatment only a slight shift to the left was demonstrable, with 18.0 per cent staff cells, 63.0 per cent polymorphonuclear cells and 19.0 per cent lymphocytes. At the same time the erythrocytes rose in number and the spleen was considerably reduced in size. Without any further treatment the almost normal blood picture persisted for about three months and subsequently the alterations of a chronic myelosis progressively recurred but so slowly that another series of irradiations was not required until after 21 months.

The second case concerned a woman aged 40, with chronic myeloid leukemia of several months' standing. At the time of her first admission colchicine was given orally and irradiation was carried out at the same time; the effect was only slight, in that the leukocytes were reduced from 400,000 to 240,000 while the differential count remained essentially unchanged. After eight months the patient had to be readmitted with a leukocytosis of 490,000. At first roentgenotherapy was instituted, without preliminary colchicine medication, and the leukocytes were reduced only to 400,000, without any appreciable modification of the differential count. Subsequently two irradiations were given after preliminary injection of 2 mg. of colchicine and the leukocytes fell to 40,000 and 10 days later to 7,800; the differential count no longer showed myeloblasts and promyelocytes, the erythrocytes became normal in number and the spleen was reduced considerably in size. This case definitely shows the superior effect of combined colchicine and roentgenotherapy over roentgenotherapy alone. The improvement lasted one year, as compared to a remission of six months after roentgenotherapy combined with peroral colchicine medication.

The third case concerned a man aged 45, with chronic myeloid leukemia, anemia, a large spleen, and perisplenitis; the leukoyctes numbered 131,000. Again oral colchicine medication combined with roentgenotherapy showed relatively little effect on 2 occasions, while after the combination of subcutaneous colchicine injections with roentgenotherapy the leukocytes fell from 180,000 to 100,000, the differential count showed a decrease of the immature cells, and myeloblasts were no longer encountered. However, six months later the patient succumbed to acute myeloblastic leukemia.

Colchicine alone has no therapeutically useful effect on the white blood cell picture but makes the young cells of leukemia more sensitive to roentgenotherapy due to its specific selective effect; thus colchicine is capable of increasing the effect of roentgenotherapy, and of making it possible in otherwise refractory cases.

Chloramphenicol in Bacillary Infections of the Urinary Tract—Garvey, Fred K., Cline, Wayne A. and Meads, Manson with the Technical Assistance of Nancy M. Haslam—*Southern Medical Journal*, 43: 85 (February) 1950.

"The patients selected for treatment with chloramphenicol were regular admissions to the clinic and wards of the North Carolina Baptist Hospital. Sixteen were females and 5 were males. Their ages ranged from 16 to 72 years. Three cases were treated with a second course of chloramphenicol three weeks after a clinical and bacteriologic relapse had occurred and are indicated as additional patient treatments in the summary of the results. Nineteen of the subjects had chronic urinary tract infection with an average known duration of 22 months; 2 others had acute infections of four and seven days respectively. Involvement of one or both kidneys was demonstrated in 18 patients; the majority of these cases were complicated also by calculi and/or hydronephrosis. Sixteen subjects had failed to respond to treatment successfully with sulfadiazine, penicillin, and streptomycin; previous therapy with aureomycin had been unsuccessful in 2 individuals.

"Extensive diagnostic studies which included retrograde pyelography, were performed on all patients. The blood hemoglobin, red and white cell counts, and the nonprotein nitrogen concentration were determined before and after treatment with chloramphenicol. Serial examinations of the centrifuged urine sediment including Gram stain and culture for bacteria, were made before, during, and after therapy. The in vitro susceptibility to chloram-

phenicol and streptomycin of the organisms that were isolated during these periods, was determined by a serial dilution method on the surface of tryptose phosphate agar plates. The concentrations of active chloramphenicol in samples of urine taken during treatment were measured by a turbidimetric microbiologic assay." The concentrations of total chloramphenicol "equivalent" in these samples were determined by the colorimetric zinc reduction procedure. In this study drug levels are termed average concentrations, as they represent the mean of the amount of chloramphenicol in aliquots of separate eight hour collections of urine taken on each respective day of treatment and during the same periods of time.

"Chloramphenicol was the only chemotherapeutic agent used during the period of observation. The following dosage schedule was utilized: A priming dose of 2 Gm. was given in two, and later in four equally divided portions to all patients. A maintenance dose of 0.5 Gm. was given at four hour intervals five times daily (omitting one morning dose at 3:00 A.M.) to patients with infections involving the upper urinary tract; 0.25 Gm. five times daily was used in 3 individuals with lower urinary tract disease only. In the early part of this study the duration of treatment was limited arbitrarily to a total of seven days. Because of frequent relapse of infection on such a regime the length of therapy was extended later to 10 or more days, depending upon the clinical and bacteriologic response of the individual patient. The total dose of chloramphenicol varied. Three patients received between 10 and 13 Gm., 12 had 18 to 22 Gm., 4 had 25 to 30 Gm., and 3 received 48 to 66 Gm.

"The response of the patients was graded in the following manner: (1) controlled, symptom free with sterile cultures of the urine for a period of at least four weeks after the conclusion of treatment; (2) improved, symptom free or clinically improved but with continued bacilluria; (3) relapsed, disappearance of symptoms and bacilluria during therapy with recurrence of either or both within one to four weeks after the cessation of treatment; (4) no effect, no change in clinical symptoms or bacilluria during treatment."

"The cases having more than one infecting organism had widespread involvement of the urinary tract. In the 11 patients whose infection was controlled by therapy with chloramphenicol and in 5 others who had a clinical and bacteriologic relapse after treatment, symptomatic improvement was rapid and dramatic, usually beginning within 24 hours after therapy was started. This clinical improvement was followed closely by the clearing of pyuria and bacilluria. In most instances the urine became microscopically free of cellular elements 48 hours after the beginning of treatment. Gram stain of the urine sediment was usually negative for bacteria 24 hours before cultures became sterile; no growth was noted 48 to 72 hours after the onset of chemotherapy. In 7 individuals who were classified as improved, reduction in clinical symptoms was paralleled by a temporary reduction in pyuria and bacilluria. Six new organisms were isolated from the urine of 5 patients three or more days after the onset of treatment with chloramphenicol. Once established, these organisms were cultured repeatedly from all subsequent urine specimens unless a bacteriologic relapse with one of the original infecting organisms occurred after treatment had ended. New species appeared in none of the patients that were classified as controlled."

In Vitro Susceptibility of Organisms.—A close correlation exists between the in vitro and in vivo activity of this antibiotic. "The colon-aerogenes group of organisms was the most susceptible. As a rule, treatment with the drug had little or no effect on strains of bacteria that exhibited a susceptibility in vitro of greater than 25 micrograms per cc. This correlation was supported also by the results of susceptibility tests performed on the new species of bacteria established in the urinary tract during therapy. All strains that were recovered were resistant to greater than 25 micrograms per cc. of chloramphenicol. Twenty-one of the 33 strains of bacteria tested before initiation of chloramphenicol therapy for their susceptibility to streptomycin were highly resistant to the latter antibiotic. Most of these organisms were recovered from patients who had been unsuccessfully treated previously with streptomycin.

"A decrease in susceptibility to chloramphenicol in vitro of fourfold or greater during treatment was noted in 9 of the 33 strains of bacteria. Two strains of *Escherichia coli* showed a fourfold and thirty-two fold increase in resistance respectively: four strains of *Aerobacter aerogenes* a fourfold, fourfold, sixteenfold, and eightyfold increase; one strain of Proteus a fourfold increase; and two strains of *Pseudomonas aeruginosa* an eightfold and sixteenfold increase respectively."

Average Chloramphenicol Concentrations in the Urine During Treatment. —"An eight hour specimen of urine from 9 of the patients with urinary tract infections was collected daily during treatment with chloramphenicol. The average active and total concentrations of chloramphenicol in aliquots of these specimens were measured." Two individuals were maintained on a dosage of 1.25 Gm. daily and 7 other cases received 2.5 Gm. daily. "The concentrations of active chloramphenicol in the urine of the latter group were higher than the former. These levels remained relatively constant for a single individual after the effect of the large priming dose disappeared but varied widely among the different subjects who were on the same schedule of treatment. Similar relationships appeared as regards the percentage of active chloramphenicol. Depending on the subject, between 14 and 40 per cent of the total drug appeared in the urine in the biologically active form. A comparison of the volume of urine output in cubic centimeters per minute and the rate of excretion of free drug in micrograms per minute suggested that these values were directly proportional up to antibiotic levels of 100 to 125 micrograms per minute. Thereafter large increases in free drug appeared which were independent of the rate of urine flow.

"Causes of Failure.—Thirteen of the 24 patients treated with chloramphenicol were classified as failures of treatment, including those cases classified as relapses. In brief, failures were noted where relatively insusceptible organisms were initially present or where they were introduced (5 cases) or developed (4 cases) during treatment. As exemplified by the following example the duration of therapy appeared also to be of importance in this regard: A 39 year old woman with a long-standing colon bacillus infection of the right kidney subsequent to renal lithiasis, was treated for seven days with a total of 18.5 Gm. of chloramphenicol. Response to therapy was prompt but relapse occurred one week after the drug had been discontinued. The infecting organisms demonstrated a degree of susceptibility that was the same as the pretreatment strain. Three weeks after relapse had occurred the patient was retreated with the same dosage schedule but was maintained on therapy for a total of 12 days and received a total of 30.5 Gm. of chloramphenicol. Again clinical and bacteriological response to therapy was prompt but the urine has remained sterile during a six week period after treatment. Underlying pathology of the urinary tract of a widespread or complicated nature has been mentioned as a factor predisposing to failure of treatment with streptomycin, aureomycin, and chloramphenicol. Such factors undoubtedly play an important role but could not be evaluated in this small series since controls with minimal pathologic involvement were inadequate in number.

"Toxic Effects.—In general, toxic symptoms were of a minor nature. The most common untoward reaction was dizziness which appeared in almost all patients who were treated on an ambulatory basis. This symptom developed several hours after the initial dose of 2 Gm. and lasted from several hours to several days. It did not appear in bed patients unless they attempted to walk about. The reaction was readily reproduced and was avoided in several instances if the priming dose was given in four 0.5 Gm. portions over a four hour period. With 1 possible exception this symptom was not severe."

"Eleven subjects complained of a bitter taste several hours after the priming dose of chloramphenicol, a symptom which apparently is produced by the excretion of the drug by the salivary glands. This symptom usually disappeared when smaller doses of the drug were given. Three subjects developed a mild, nonitching, maculopapular eruption over the forehead and malar eminences of the face. The rash was reproduced during a second course of the drug in 1 instance. In this individual, intradermal skin tests with an aqueous solution of chloramphenicol were negative and precipitins against the drug did not appear

in the serum. A mild diarrhea, glossitis, or eosinophilia appeared in single patients during treatment. They disappeared promptly when therapy was discontinued. No change was noted in the concentrations of nonprotein nitrogen in samples of blood taken before and after treatment. Except for the 1 instance of eosinophilia, there were no significant variations in the red and white cell counts and hemoglobin values in the blood."

Relation of Acute Hepatitis to Cirrhosis of the Liver — PATEK, ARTHUR J., JR. — *American Journal of Medicine*, 8: 267 (March) 1950.

"The ultimate course of patients with signs of protracted viral hepatitis has been a subject of interest and concern. It seems fairly certain that the majority of patients with mild, persistent symptoms, whose liver biopsies show moderate periportal inflammation with slight fibrosis, will recover completely. However, there remain a few who show signs of progressive deterioration and die of cirrhosis which has been described as of various types. . . . Three types of cirrhosis have been described as sequelae to viral hepatitis: (1) postnecrotic, (2) cholangiolitic and (3) Laennec's."

"Postnecrotic or coarsely nodular cirrhosis differs from subacute yellow atrophy only in the longer time interval from the initial hepatitis to the stage of liver failure. Whereas subacute yellow atrophy generally runs a fatal course within a few weeks or months, the identical pathologic findings have been seen in patients surviving years after the initial hepatitis. The writer has observed 15 cases (7 proved, 8 presumptive) with survival from 6 months to 13 years after the onset of the illness. The disease was latent or unrecognized in several of these cases before signs of liver failure appeared. Once failure occurred there was a progressive downhill course. The fact that the pathologic features of postnecrotic cirrhosis remained true to type even though the initial hepatitis took place years before suggests that there is no tendency for this type to develop into the Laennec type of disease. The development of postnecrotic cirrhosis bears no relation to the severity of the initial attack. This suggests either that the virus may remain active in these patients or that some other process prevents the resolution and repair of the acute hepatitis.

"Another form of cirrhosis that is being seen more frequently than in the past is cholangiolitic hypertrophic biliary cirrhosis. In these patients intermittent fever, jaundice, pronounced hepatosplenomegaly and abdominal discomfort usually continue for years before the onset of failure. Laboratory tests suggest extrahepatic biliary obstruction because of increased serum cholesterol and alkaline phosphatase, and frequently a negative cephalin-cholesterol flocculation reaction. The liver cells at first appear to be relatively normal but there is fine intralobular fibrosis and cellular infiltration about the small bile ducts and portal radicles. The fatal termination is characterized by cholemia, at times complicated by hemorrhage or ascites formation. The possibility remains that this is a separate entity. The clinical features and pathology are peculiar. They recall certain cases of sensitivity to arsenicals in which intrahepatic biliary tract obstruction has been described. Is it possible that cholangiolitic cirrhosis represents a chronic sensitivity reaction primarily within the smallest bile radicles with subsequent changes in the liver cells?

"In most reported series of Laennec's cirrhosis the incidence of ancient jaundice has varied from 7 to 13 per cent. However, in a more recent series 33 per cent of the patients gave a story of antecedent jaundice as compared to 7 per cent of a control hospital population. The question properly was raised as to whether infectious hepatitis may have led to Laennec's cirrhosis in these cases. The explanation is not clear. It is conceivable that patients with subclinical Laennec's cirrhosis are more susceptible to intercurrent hepatitis than the general population.

"In reports on puncture biopsies of the liver, cirrhotic changes have been described as a sequel to acute hepatitis. From the small sections obtained it is not always possible to define these positively as Laennec's cirrhosis. The cases have been few and the likelihood exists in certain instances that cirrhosis may have antedated the episode of acute hepatitis. At the present time there seems to be insufficient evidence to indicate that infectious hepatitis per se leads to Laennec's cirrhosis."

Sustained Anuria in Lower Nephron Nephrosis. Report of 2 Cases Treated Conservatively with Recovery— FOWLER, NOBLE O. AND HUNT, W. E.—*Annals of Internal Medicine*, 32: 477 (March) 1950.

"Two cases of lower nephron nephrosis surviving under conservative management despite anuria of 10 days and 11 days are reported. . . . These 2 cases illustrate the fact that man can live anuric for 10 and 11 days without the use of artificial methods to remove urea and toxic products from the blood; since diuresis usually occurs spontaneously by the eleventh or twelfth day, it would seem that some question could be raised as to the need for such methods as peritoneal lavage or artificial kidney in the treatment of the anuria of lower nephron nephrosis." The term "anuria" in this paper is not used in its strict literal sense, but as indicating a urinary output of less than 100 cc. per 24 hours.

Case 1.—A 43 year old white male refrigerator mechanic was admitted to hospital for the first time on December 13, 1947.

"For four months preceding admission, the patient had used carbon tetrachloride in cleaning refrigerator parts for half an hour or so once or twice weekly. A week prior to admission, he began to consume large quantities of alcoholic beverages. The day before he became ill, he worked all day in a closed room, 32 by 64 feet, using carbon tetrachloride to clean refrigerator parts. There was in this same room an open pan of carbon tetrachloride the entire day. That night, the patient did not feel well. He drank a few bottles of beer and took one drink of whiskey, following which he vomited. The next morning, he developed a constant aching epigastric pain accompanied by persistent vomiting. Oliguria and dark urine were noted this same day. The patient came to the hospital late that same night and was admitted. Past history revealed mild chronic alcoholism and an attack of severe right upper quadrant pain three weeks prior to admission; this pain had required morphine for relief."

"On admission, temperature, pulse, and respirations were normal. The only positive physical findings were a blood pressure of 135/80 and a large tender liver felt 3 fingerbreadths below the right costal margin.

"Laboratory Data on Admission: Hemoglobin 17 Gm.; red blood cells, 5,230,000; white blood cells, 12,200; 85 per cent polynuclears, 13 per cent lymphocytes, 1 per cent eosinophils, and 1 per cent basophils. Urine: *p*H 4.5; albumin, 3 plus; loaded with white blood cells, positive for bile. Kahn test, negative. Blood urea nitrogen, 16 mg. per 100 cc. of blood. CO_2 combining power 44 volumes per cent. Blood chloride 528 mg. per 100 cc. of blood. Serum amylase 91 units. Chest x-ray: heart of normal size; lung fields clear."

Course: "The patient was virtually anuric for the first 10 hospital days. Because of this, an attempt was made to restrict fluids to the output plus 1,000 cc.; this attempt was not always successful. . . . Because of persistent vomiting, most feeding was done parenterally.

"On the third hospital day, the patient was noted to be slightly icteric, and one vascular spider was noted on the left chest. On this day, cephalin flocculation test was 4 plus in 24 hours, and total serum bilirubin was 2 mg. per cent. The bromsulfalein test (5 mg./kilo) on this date showed 47 per cent retention in 45 minutes. A lumbar puncture was negative on the fourth day. The patient was afebrile for the first four hospital days. On the fifth day, retrograde pyelograms were done, and the patient began to run a low grade fever. The pyelograms were normal. Penicillin was given for the next week; fever gradually subsided during this period. On the sixth day a liver biopsy showed central necrosis and fatty degeneration. On the seventh day, the heart was slightly enlarged to percussion, and the pulmonic second sound was accentuated. The patient was digitalized on this day because it was felt that he was developing early congestive heart failure. A chest x-ray on the eighth day showed moderate cardiac enlargement and early pulmonary edema. There was no actual pitting edema at any time, but the patient's face was felt to be fuller.

"On the ninth day, a pericardial friction rub was first noted; this was thought to be due to uremia, since the blood urea nitrogen was 135 mg. per 100 cc. of blood at this time. Electrocardiogram on this

day showed nonspecific T wave changes. Hemoglobin on this day reached its nadir —11 Gm. On the eleventh hospital day there were pain and swelling in the left deltoid region, perhaps the result of penicillin. On this day, the urine output first rose above anuric levels, and increased steadily thereafter. . . . Chest x-ray on this day showed a further increase in both the size of the heart and in the pulmonary edema. In spite of the rising urinary output, the patient was quite ill on the thirteenth day, being drowsy, but never stuporous, and hiccuping frequently. Some benefit from the use of CO_2 inhalations was noted with regard to the latter symptom. After this day, the patient gradually recovered his appetite and normal mental status. On the sixteenth day, the urine became negative, and remained so. On the seventeenth day, the serum bilirubin had returned to normal. On the twenty-first day, the chest x-ray showed the heart to be still generally enlarged, but the lung fields to be somewhat clearer than before. On the twenty-fifth day, the electrocardiogram was consistent with pericarditis. On the twenty-seventh day, chest x-ray and fluoroscopy showed the heart to be still enlarged, with a large left ventricle. The lung fields were clear. On the twenty-eighth day, the patient developed a pain in his right chest and a fever of 102 degrees. Penicillin was then started and continued for five days. The patient was free of pain and fever on the thirty-first day. On that day, chest x-ray showed the heart to be moderately smaller than on the preceding film. On the thirty-sixth day, the pericardial friction rub had disappeared. Phenol red test on the forty-first day showed excretion of 8 per cent of the dye in 15 minutes and a total of 47 per cent in 2 hours. On the forty-third day, urinary concentration test showed a maximum concentration of 1.018. Hemoglobin had risen to 12.5 Gm. on this day. On the forty-fifth day, venous pressure was 8 cm. of water, and decholin circulation time was 15 seconds. The patient was discharged on this day, his heart being still enlarged." No further information with regard to his course has been obtainable.

Case 2.—A 42 year old white female stenographer was admitted to the hospital on June 3, 1947. "The history essentially was that of low back pain of two years' duration with recent radiation into the left leg.

"Physical examination on admission was normal except for findings suggestive of herniated intervertebral disk and radiculitis of the first sacral nerve.

"Laboratory Data on Admission: Hemoglobin 12.5 Gm.; red blood cells 4,150,000; white blood cells 8,550; 58 per cent polynuclears, 37 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils. Sedimentation rate of erythrocytes, 5 mm./hr. Bleeding time 1.5 minutes. Clotting time 3.5 minutes. Urinalysis negative.

"Course: On the eighth hospital day, a myelogram revealed a filling defect at the fifth lumbar interspace. On the fourteenth hospital day, a partial hemilaminectomy was performed and the degenerated fibrocartilage was removed. There was considerable bleeding from the epidural space, and the blood pressure fell to 60/45; 500 cc. of whole blood and 25 mg. of ephedrine sulfate were given and the blood pressure then rose to 200/100 and remained there. Two hours postoperatively, the blood pressure began to fall again, and considerable bleeding was noted from the operative site. The hemorrhage was controlled with some difficulty. At this time the patient received 2,500 cc. of plasma and 500 cc. of whole blood for shock."

"On the first postoperative day, the blood pressure fell to 88/30, although there was no further evidence of hemorrhage. The patient was given 1,000 cc. of whole blood and 2,000 cc. of normal saline intravenously, with return of the blood pressure to normal levels. The total urinary output for this day was 125 cc., and the patient was virtually anuric for the next nine days. Because of the anuria, a check was made, with regard to the type blood given the patient; it was later found that the original transfusion had been mislabeled as to type. On the second postoperative day, hemoglobin was 9 Gm. per 100 cc. of blood, and platelet count was 55,000 per cu. mm. The patient received a total of 3,000 cc. of fluid parenterally on this day, including 1,000 cc. of whole blood. That evening, she developed pulmonary edema and mild cyanosis. On the third postoperative day, the patient had frank pulmonary edema, which was treated with

oxygen. Platelet count on this day had risen to 281,000, and thereafter remained at normal levels. The patient was improved clinically on the fourth postoperative day. On the fifth postoperative day, bilateral sympathetic block was performed in hope of improving kidney function, but anuria continued. On the next four days, the patient was fairly comfortable, free of edema, but intermittently delirious. On the tenth postoperative day, generalized edema appeared, and the patient became dyspneic; the blood pressure rose to 160/60. On the eleventh postoperative day, the patient was in severe congestive heart failure, which improved somewhat after digitalization with cedilanid. Diuresis seemed well under way on the twelfth postoperative day, with a total urinary output of 900 cc., but improvement was delayed. On the thirteenth day, the patient exhibited anasarca, marked venous distention, frothy sputum, and appeared moribund. A phlebotomy with removal of 500 cc. of blood was followed by considerable improvement. On the fourteenth postoperative day, she was able to be out of oxygen intermittently, and thereafter made a rapid recovery. All edema disappeared in the succeeding three days. The urinary specific gravity remained in the vicinity of 1.010, and in spite of the marked clinical improvement on the part of the patient, her azotemia remained essentially unimproved for several days. A normal blood urea nitrogen was not reached until the thirty-sixth postoperative day, at which time the patient was up and about, and was asymptomatic.

"On July 28, phenol red test showed 75 per cent excretion of the dye in two hours. On August 8, urea clearance was 70 per cent. On August 18, the Mosenthal test showed urinary specific gravities ranging from 1.008 to 1.016. The patient had developed a severe anemia, which was gradually improving as she was discharged asymptomatic on August 21, 2 months and 18 days after admission.

"These 2 cases are not presented as examples of ideal management of the anuria of lower nephron nephrosis. . . . In neither of these cases was there any attempt to force diuresis by administration of excess fluids, yet pulmonary edema made its appearance in both patients, and almost caused death in the second patient. This fact indicates the need for even more careful restriction of fluids in the anuric patient than was observed in these patients."

"The anuric patient should be fed by mouth if possible. He should receive only a few hundred cubic centimeters of fluid daily; if he must be fed parenterally, the fluid should contain as much dextrose as possible up to 6 Gm. per Kg. per 24 hours, 2.5 Gm. of sodium chloride, 2 mg. of thiamine, 5 mg. of riboflavin, 20 mg. of niacinamide, and 100 mg. of ascorbic acid. The total water and sodium chloride intake should be increased if there is vomiting, diarrhea or visible sweating."

Streptomycin and Tuberculosis. Clinical Experience — Albertal, Manuel, Dobric, Leonardo L. and Rodrigue Olivares, J. E. — *La prensa médica argentina*, 37: 53 (January 6) 1950.

The authors report their experiences with an unselected material of 115 cases of pulmonary tuberculosis, treated with streptomycin and a rigorous sanatorium cure, based on absolute bed rest and dietetic and hygienic measures. The age ranged between 17 and 65, and most patients were between the ages of 21 and 36. Age did not seem to influence results of treatment or tolerance to the drug. The benefits derived from streptomycin treatment seem to depend on early institution of treatment although the relation is not strictly mathematical; it seems most definite in hematogenic forms in which early treatment may prevent phthisic development. After retrocession of all hematogenic elements only cavitary formations may remain, developed by focal progression. Evidently the length of time before treatment is related to the development of the lesions and early bacteriostatic action on the germs will permit organic repair which will be the more complete and rapid the less advanced the tissue damage.

Of the 115 patients, 26 died, 21 abandoned treatment and 68 finished it. Abandonment of treatment was only exceptionally caused by intolerance to the drug. Some of the deaths were caused by fulminating hemoptyses, suffocating spontaneous pneumothorax and progression of extrapulmonary lesions, particularly intestinal ones, after definite improvement had been ob-

tained. No benefit or only highly transitory benefit was derived from the treatment in 13 cases.

The first group included 32 cases of chronic reinfection tuberculosis, excluding the acute severe exudative forms; the general condition improved in almost all of them, with a gain of weight and diminution of the toxic and functional symptoms, and in some cases the roentgenologic findings improved to such an extent that collapsotherapy became possible. Cavities showed diminution of size, cleansing of their walls and some regression but cure of cavities was not obtained with streptomycin treatment alone. In cases in which the roentgenologic findings suggested a mechanical bronchial component, regression was not as persistent and definite as expected. There were 6 deaths in this group, 8 patients abandoned treatment, 11 were improved and 7 derived no benefit.

The second group included 23 cases of hematogenic dissemination, with or without extrapulmonary manifestations; this group represents one of the most definite indications of streptomycin treatment. There was definite regression in all strictly pulmonary cases, and complete remission was obtained in cases treated before phthisic development. In extrapulmonary forms appreciable benefit was obtained with respect to the pulmonary component. Hematogenic cavities responded more favorably than others but hematogenic disseminations with phthisic development frequently require collapsotherapy as the phthisic lesions are not much influenced by the streptomycin although the dissemination is controlled. There were 9 remissions and 11 improvements, while 2 patients did not benefit and 1 died. Prolonged observation is most satisfactory in this group in that clinical and roentgenologic improvement with regression of the lesions and functional recovery from associated laryngeal lesions persisted for two years in some cases.

Chronic hematogenous dissemination with phthisic lesions of the apex, sclerosis and emphysema did not benefit, and cavities with scleroemphysema require collapsotherapy.

The third group included 29 cases of bronchogenic dissemination of an acute exudative type, including pneumonic forms and canalicular spreads of chronic reactivated lesions. The results varied; thus canalicular dissemination was not prevented in a case at a time when streptomycin resistance could not yet have developed but the dissemination seemed more benign. Recent bronchogenic dissemination was definitely influenced, while lobitis was less rapidly and intensely influenced, leading to cavity formation in spite of treatment. Pneumonic and bronchopneumonic forms derived little benefit, but the time factor seems to play an important part in such cases. There were 2 remissions and 11 improvements in this group, while 3 patients did not benefit, 5 abandoned treatment and 8 died.

The fourth group included 11 cases of typical initial infiltrations regardless of localization, and results were highly gratifying in this group, provided treatment was instituted early. Out of 5 cases treated early 2 showed complete remission and 3 showed marked clinical and roentgenologic improvement, while of 6 cases treated with some delay 3 patients died from progression and fulminant hemoptysis and 3 abandoned treatment. In all cases of this group in which activity of the process is not promptly controlled by the streptomycin treatment combination with collapsotherapy is indicated.

The material further included 4 cases each of empyema and pleurisy, 7 of polyserositis, and 5 of meningitis. No prompt absorption of pleural effusions of artificial pneumothorax treatment was obtained by streptomycin treatment, whether only endopleurally or in combination with intramuscular injections. In some cases analysis of the pleural gases showed that a bronchopleural fistula existed and accounted for the inefficacy of the treatment. Pleural effusions were also little influenced when being manifestations of hematogenic dissemination, and 2 such patients subsequently developed fatal meningitis. In serofibrinous pleurisy, however, streptomycin treatment seemed to shorten the febrile toxic period and to produce rapid complete absorption. In polyserositis and peritonitis streptomycin treatment proved ineffective, but had not been started until after the condition had developed over a long period of time.

The low effect of endopleural streptomycin treatment has been linked to the in-

hibitory effect of an acid medium on the bacteriostatic action of the antibiotic; conversely paraamino salicylic acid is more effective in tuberculous pleurisy and empyema. However the authors believe that other reasons play a part, connected with the patient's immunologic condition and the clinical form of the affection. The hematodromic component seems to play an important part, and the highly vascularized lung tissue is more readily reached by the antibiotic than the meninges and pleurae when highly altered by inflammatory and exudative processes. The condition of immunity and hypersensitivity also plays a part and the improvement obtained by streptomycin treatment as well as by older methods should be used to carry out surgical treatment under optimal conditions, particularly in the case of empyema. Of the 20 cases of these types, only 1 showed remission, 5 showed improvement, 1 did not benefit, 5 abandoned treatment and 8 died.

In tuberculous meningitis the authors recommend streptomycin intramuscularly and paraamino salicylic acid intraspinally, but when there was blockage the intracisternal pathway was used with streptomycin rather than paraamino salicylic acid.

Diabetes did not prove any obstacle to streptomycin treatment and the results were comparable to those in nondiabetics although severe forms are more frequent; 8 such cases were included. Five pregnancies were included and 4 ended in term and 1 in a premature delivery.

The toxic reactions diminished, due to purer preparations and to the fact that the daily dose hardly ever exceeded 1 Gm.; antihistaminics were given whenever toxic symptoms appeared or were imminent, as they have been shown to prevent acoustic nerve lesions. In several cases treatment had to be discontinued but could be continued with dihydrostreptomycin. The toxic threshold of the latter is much higher than that of streptomycin provided the renal function is good. Reactions of a histaminic type were not observed. Local irritability occurred in 12 cases. Allergic reactions included fever in 9 cases, urticaria in 3, and rash in 2 cases, while the serum disease type was not observed. Renal alterations in the form of transitory oliguria occurred in 2 cases while albuminuria and casts were not observed. Neurotoxic manifestations included 18 cases of headache and nausea, 7 of malaise and dizziness, and 1 each of tinnitus with hypacusis and with hyperacusis.

The daily dose of 1 Gm. was first divided into six injections, later into four, and finally into two injections; analysis of the results shows that a daily dose of 18 mg. per Kg. weight is optimal.

Streptomycin treatment should be combined with medical or surgical collapsotherapy whenever indicated; 1 case in which collapsotherapy could not be carried out because of the results of functional studies of the respiratory tract showed reactivation seven months after discontinuation of treatment, demonstrating that not too much confidence should be placed in streptomycin treatment alone and that it should be considered an excellent coadjuvant to other effective methods.

Paraamino salicylic acid has been available for combination with streptomycin treatment for only a short period of time and the influence of the combination on the appearance of germ resistance cannot be evaluated as yet, but this combination seems highly effective. Streptomycin treatment before and after surgical collapsotherapy seems to protect the patient better against postoperative disseminations and reactivations.

Whenever collapsotherapy is not feasible regressions obtained with streptomycin treatment should be considered as such rather than as cures and the classical sanatorium treatment should be instituted for as long periods of time as classically advised. Streptomycin treatment should be considered a coadjuvant and for extension of the indications of medical and surgical collapsotherapy.

In acute severe bronchopneumonic forms streptomycin treatment does not influence the clinical and roentgenologic aspects but seems to prolong life. This phenomenon was more marked in chronic tuberculosis in which a period of stabilization and improvement and even negativization of the sputum was followed by a slow progressive course leading to a degree of cachexia never observed before; the impression was created that the bacilli remained present but were unable to act, and that death was due to extensive organ destruction, paren-

chymatous degeneration and nontuberculous secondary lesions.

The difference in effect on early treated hematogenous cases, and on such cases is intimately linked to the mode of action of the antibiotic which has been shown to interfere with the development and multiplication of the sensitive germs while there is no influence on the repair processes of the tissues. This accounts for the beneficial effects in early hematogenous disseminations with only beginning focal reaction and for the lesser effect in chronic tuberculosis with extensive destructions and secondary processes; it also accounts for the good results in typical infiltrations provided treatment is started early before destruction supervenes.

Prothrombin Estimation and Dicoumarol Therapy — TOOHEY, M. — *British Medical Journal*, 1: 518 (March 4) 1950.

"Estimation of prothrombin has assumed a greater clinical significance since the use of dicoumarol. Practical difficulties in carrying out the test are mainly due to the inability to standardize and prepare thromboplastin. Quick's method is a simple one, and most convenient for clinical use. The commonly used method of diluting whole plasma with saline in order to bring out an early fall in the prothrombin level is not advocated.

"A simple method of preparing a stable and active thromboplastin preparation is essential. The most frequently used preparations are Quick's original acetone-dried brain extract and Russell-viper venom. The latter often gives false low clotting times, with the consequent danger of overdosage with dicoumarol and subsequent haemorrhage. Preparation of acetone-dried brain extract usually requires skilled technical ability."

For the last seven years the writer has used saline emulsions of human brain extract with consistently good results. "The main advantages are the ease of preparation, the stability, and the consistent results obtained."

"Fresh human brain is used, as it is readily obtained from the postmortem room. Human brain extract also keeps for longer periods than rabbit brain. It is freed of all membranes and blood vessels and washed in saline. A small portion, enough to cover a shilling, is emulsified in a mortar with approximately 20 ml. of normal saline to which has been added 0.5 per cent of phenol as a preservative. The emulsion is filtered through gauze to remove all gross particles and the resulting solution should be of milky opacity. When this is tested with normal plasma it invariably gives a clotting time of 10 to 15 seconds. This emulsion, however, contains a considerable excess of thromboplastin, and, while it will normally give good and reliable results with low prothrombin plasma, it tends in some cases to inhibit clotting and may occasionally for this reason give falsely high clotting times." The writer therefore dilutes the emulsion to a weaker concentration.

"A convenient method of dilution is to prepare a solution which is approximately equivalent to that in the tube containing 150 mg. of protein as used for estimation of cerebrospinal fluid protein. This concentration (150 mg.) will give a clotting time of 13 to 16 seconds with normal controls.

"It will be found that the 150 mg. thromboplastin solution will tend to decline in activity to the extent of only three to four seconds over a period of a month, and many preparations will keep for much longer. Several have kept for as long as six months, with a prolongation of only five to six seconds with normal plasma. Many of the more concentrated thromboplastin preparations have remained stable for one year, with a prolongation from the initial clotting time of only five to six seconds. The weaker the initial concentration of thromboplastin preparation the quicker it tends to become inactive. The simplicity with which these preparations are made renders it unnecessary to keep them for long periods.

"It is essential that, in preparation, the emulsion be thoroughly shaken for at least five minutes so that the thromboplastin goes into solution. The preparations are kept in a tightly stoppered container at 4° C. Before use they should again be thoroughly shaken and be left at room temperature for 15 minutes." The addition of 0.5 per cent phenol to the saline pre-

vents bacterial contamination, which the writer has found is a common cause of rapid deterioration of these saline-brain emulsions. In his opinion it is not necessary to prepare dried brain extract, thus greatly simplifying prothrombin estimations.

"The difficulty encountered in prothrombin estimation lies in expressing results and also in deciding to what extent the level of prothrombin should be lowered. Most authorities recommend a lowering to between 10 and 30 per cent of normal—a safe level, as bleeding seldom occurs when the prothrombin content is above 10 per cent. Some authorities recommend a prolongation of the clotting time to twice the normal; this roughly corresponds to 20 per cent of normal. The difficulty in practice of expressing a definite percentage of normal is that prothrombin clotting times will vary according to the prothrombin content of the plasma and also with the concentration of thromboplastin used." A much simpler interpretation which is of benefit to the clinician can be adopted.

"(*a*) A thromboplastin preparation made as described above, which will give a normal clotting time of 13 to 16 seconds, is used." The writer does not employ a preparation which gives a normal clotting time of above 20 seconds, as at that level it tends to decline in activity too rapidly, and it is important to be certain that the thromboplastin is active. Conversely, the writer does not advocate a more concentrated preparation of thromboplastin with its much shorter clotting times, usually 10 to 12 seconds, as this strength is not optimal for low prothrombin plasmas and may give false longer times. A saline emulsion of brain diluted to 150 mg. of protein will be found in practice to be most convenient.

"(*b*) The prothrombin level of the patient on dicoumarol should be maintained between 30 and 50 seconds, using the above thromboplastin preparation." With more than 50 seconds one is veering to the danger level, though many patients have given clotting times of 60 to 70 seconds without haemorrhagic manifestations. "In a carefully controlled series of 30 patients treated with dicoumarol the shortest clotting time found with haemorrhage was 85 seconds." The writer considers the absolute time to be of greater importance than a percentage reading, as, when preparing prothrombin percentage curves, plasma is diluted with saline or prothrombin free plasma, which is an artificial procedure in that one may well dilute other factors taking part in blood coagulation that does not bear a direct relation to what happens in vivo.

The writer does not recommend making prothrombin estimations on diluted plasma, which many authorities do in order to bring out a minor reduction in prothrombin content. "In actual practice bleeding has never occurred with a clotting time of less than 50 seconds."

Dicoumarol Therapy.—Dosage: There is no standard dose of dicoumarol, and the reactions vary greatly with different patients. "For this reason it is essential that prothrombin estimations should be carried out at regular intervals. Many workers recommend daily estimations." The writer has found that estimations on alternate days are sufficient, except during the initial stages of treatment—that is, for the first four or five days—and in those cases with widely fluctuating clotting times that sometimes occur. "One factor of great importance with regard to dicoumarol dosage is the age and general condition of the patient." The older and more frail the patient is, the more susceptible is he to dicoumarol—so much so that the writer gives a reduced dosage to all those over 65 years. "Of 6 patients who had haemorrhages all but 1 were over 65. It is important to remember that some patients are much older than their years, and vice versa; and this factor should be borne in mind when using dicoumarol. Some patients are very susceptible to dicoumarol, and haemorrhages can occur with a very small dose; 1 patient, aged 69, had serious bleeding with a total dose of only 550 mg. of dicoumarol.

"Scheme of Dosage: For younger patients: first day, 300 mg.; second day, 200 mg.; third day, 200 mg.; and then a daily dose of 50 mg., to be varied according to the prothrombin clotting time. Many young robust people are relatively insensitive to dicoumarol and will need larger doses—for example, 100 mg. daily instead of 50 mg. to keep the prothrombin at a

therapeutic level. For older patients (65 years and over): first day, 200 mg.; second day, 200 mg.; third day, 100 mg.; and then 50 mg. daily, to be varied according to prothrombin clotting time. In the initial stages it is better to give dicoumarol in small divided doses than in a single large dose.

"Most authorities usually give an initial dose of 300 mg. of dicoumarol followed by 200 mg.; they then give it according to the prothrombin content as ascertained by daily estimations." This method tends to produce a fluctuating curve. The writer therefore prefers to give a small daily dose of dicoumarol after the initial heavier dosage—omitting the drug, of course, if the prothrombin falls to a dangerously low level.

In practice the writer has found the daily microscopical examination of urine for red cells very useful. "In many cases their presence foreshadows an impending gross haemorrhage, and as soon as any quantity appears dicoumarol must be stopped."

Rate of Disappearance of Prothrombin from the Circulation — STEFANINI, MARIO AND PISCIOTTA, ANTHONY V.— *Science*, 111: 364 (April 7) 1950.

New techniques for the study of the speed of disappearance of prothrombin from the circulation have become available with the introduction of methods for direct determination of the concentration of prothrombin, and for simple preparation of concentrates of prothrombin. "The problem was, therefore, investigated in rabbits, in which prothrombin concentration had been drastically depressed with dicumarol treatment.

"Five male rabbits of average size received daily 10 mg./Kg. body weight of dicumarol in gum acacia suspension, introduced in the stomach by intubation." After five days of treatment the prothrombin level of the animals was usually lower than 5 per cent normal, while the concentration of the labile factor, determined with the method described by Quick and Stefanini, appeared normal or slightly decreased. At this point, the writers injected intravenously in each rabbit a freshly prepared concentrate of prothrombin, obtained from a volume of fresh oxalated rabbit plasma equal to that of the presumed plasma volume of the animal under investigation. "For working purposes, this was considered equal to 5 per cent of the body weight of the animal. No reaction or untoward effect was noticed. The prothrombin time was then determined in plasma obtained by centrifugation at 2,000 r.p.m. for 10 minutes of oxalated blood collected from the central artery of the ear at various intervals after the injection (30 minutes, and 1, 6, 12, 24, 36, 48, 60, and 72 hours). During this phase of the experiment the rabbits continued to receive 5 mg. of dicumarol per Kg. body weight daily to prevent any formation of prothrombin by the liver." The concentrate of prothrombin was prepared by the method of Quick and Stefanini, the only modification being that the final product was treated with 1/10 vol. of full strength thrombin to remove the fibrinogen still present, stored at 4° C. for 1 hour, and then incubated in a water bath at 37° C. for 30 minutes in order to inactivate any remaining thrombin. "The prothrombin time was determined with the one stage method of Quick and its values were checked by determining the concentration of prothrombin directly with the technique described by Quick and Stefanini. The results of the two procedures usually agreed within ± 5 per cent."

"Restoration of the prothrombin level to almost 100 per cent of normal followed immediately the injection of the concentrate of prothrombin. About 50 per cent of the prothrombin injected disappeared from the circulation within the first 12 hours, and about 80 per cent in 24 hours. From this time on, a slow depletion continued until the original level was again reached, 48 hours to 60 hours after the injection.

"These findings show that prothrombin is promptly utilized or metabolized in the body, most of it disappearing from the circulation in the first 24 hours." The results also demonstrate that the concentrate of prothrombin prepared with the technique developed in the writers' laboratory is capable of restoring to normal the prothrombin concentration of dicumarolized rabbits, in a definite quantitative relationship.

A New Improved Method for Determination of Prothrombin Levels in Blood — GOLDFEDER, ANNA, BLOOM, DAVID AND WEINER, MURRAY—*Science,* 111: 365 (April 7) 1950.

A simplified and accurate procedure for blood cell counts and hemoglobin determinations has been developed for experiments on mice. Its advantages over previous methods are greater precision and increased saving of time, effort, and expense. It differs from similar procedures in that it uses calibrated capillary tubes instead of the conventional pipets. "The use of these tubes, in addition to some technical adjustments, resulted in a reliable, practical method for the estimation of prothrombin activity."

The procedure is as follows: Capillary tubes are filled with a 2 per cent solution of potassium oxalate which is evaporated to dryness in the oven. "A suspension of rabbit lung thromboplastin is prepared according to the Link-Shapiro modification of Quick's method except that a stronger calcium chloride solution (0.125M), and whole blood, instead of plasma, are used. The blood is taken into tubes with dry rather than dissolved oxalate. Then 15 cu. mm. of the thromboplastin solution is placed on a clean glass slide. A 5 cu. mm. oxalated capillary tube is filled with blood from the mouse tail. The oxalated blood is quickly pressed out into the thromboplastin on the glass slide with the aid of a minute rubber bulb, of the type used for smallpox vaccinations, and the blood and thromboplastin are mixed gently. The stop watch is started at the same instant that the blood is added to the thromboplastin. The mixture on the glass slide is drawn in and out of the capillary tube by gently pressing the rubber bulb, avoiding air bubbles. At each filling, the capillary tube is lifted up slightly to permit observation of the formation of the fibrin strand. The latter can be noticed suddenly, giving a clearly defined end point of blood clotting. When it appears, the stop watch is instantly stopped and the time is noted. Table 1 summarizes the results obtained by the use of this method on normal Swiss white mice.

"The method has proved to be simple, reproducible, and economical. A major advantage is that the test can be performed promptly and with small volumes (5 cu. mm.) of blood, thus avoiding the necessity for venipuncture. In small species, such as mice, it permits repeated determinations on the same animal with only negligible trauma to the tip of the mouse tail and loss of only insignificant volumes of blood. In man, the method permits the bedside determination of prothrombin time from blood obtained by finger puncture. However, the method introduces two new variables which warrant consideration. (1) Since the method uses whole blood, subjects with low hematocrit values may have greater plasma volumes per aliquot of whole blood. (2) The test is performed at room temperature rather than in a constant temperature water bath. These factors may cause small but significant variations, which may be corrected or taken into account in problems calling for greater accuracy. The relatively narrow range of average deviation indicates that the technique is sensitive and reliable."

Table 1

Prothrombin Levels of White Mice, Swiss Strain

No. of Mice	Determinations	Temp. in °C	Prothrombin time in sec: lowest	highest	mean	Deviation	Remarks
40	40	23	19	31	28.4	2.7	Single determinations
9	20	26.5	20	32	24.9	2.5	Repeated determinations
7	18	28.5	18	24	22.9	3.7	within 3 days, at 24 hr. intervals

Effect of Free and Combined Available Residual Chlorine upon Bacteria in Swimming Pools — Mood, Eric W. —*American Journal of Public Health*, 40: 459 (April) 1950.

"One purpose of sanitary control of swimming pools is the maintenance of some fixed amount of residual chlorine, which will kill bacteria as they are washed into the water from the bathers' bodies rapidly enough to prevent conditions of gross pollution." The joint committee of the Conference of State Sanitary Engineers and the American Public Health Association recommended a residual chlorine concentration of 0.4 p.p.m. to 0.6 p.p.m. when the pool was in use, and 0.7 p.p.m. to 1.0 p.p.m. for residual chloramine. This latter figure has been modified to suggest the desirability of operating with higher chloramine residuals up to 2.0 p.p.m.

A study was undertaken to measure the relative effectiveness of free and combined available residual chlorine as bactericides in swimming pool water. "To obtain this measurement it was decided to use tests for the number of bacteria which grow on agar at 35-37° C., coliform bacteria and streptococci."

For this study, four pools were selected. "Each pool was operated in accordance with the requirements of the Joint Committee Report and were of the continuous recirculation type. All pools used fresh water and three were located indoors. Although combined residual chlorination through the use of ammonia gas was not the practice by intention, one pool applied aluminum ammonium sulphate and actually obtained this method of disinfection and a second pool changed to it accidentally during the test period by changing coagulants.

"Each of the four pools was tested on three occasions making a series of 12 tests within this study. Before each test, the residual chlorine content was measured to insure reasonable adherence to the minimum and maximum standard for disinfection as set forth in the Joint Committee Report. The amperemetric titration was used in preference to the orthotolidin-arsenite test to measure free and combined available residual chlorine because the high temperatures of swimming pool waters cause the color reaction of chlorine and orthotolidin to occur too quickly for accurate results.

"The sampling procedure for the 12 tests was identical for each occasion. The pool was closed to swimmers at least one hour before the start of the test to permit the purification processes to reduce the bacterial content to a practical minimum. Just before the start of the test, samples were collected and titrated with the amperemetric titrator to determine the quantity of free and combined available residual chlorine present. Three sampling points were used; one at the midpoint of the shallow end and two on the sides, one-third the distance from the shallow end toward the deep end. At the start of the test period the bathers lined up around the edge of the pool at equal intervals. The initial bacteriological samples were collected at the three sampling points, and then at a given signal all bathers dove into the pool and swam for 5 minutes. Additional samples for bacteriological analyses were collected simultaneously from the three sample stations at the following intervals, timed from the moment the bathers entered the water: ½, 1, 1 ½, 2, 2 ½, 3, 4, and 5 minutes. At the end of the 5 minute swim period another signal was given to the bathers to withdraw quickly from the water, and, following an interval of 5 minutes more during which no bathers were allowed to go into the water, a final set of samples was collected.

"The bacteriological samples were analyzed promptly after collection." The tryptone glucose extract agar plates were incubated at 35-37° C. for 48 hours. "Duplicate plates of 0.1 ml. and 1.0 ml. dilutions were poured for each sample. Two per cent brilliant green bile broth was used as the confirmatory medium for coliform bacteria.

"The results from the series of 12 tests were placed in one of two categories, those collected from swimming pool water containing free available residual chlorine equal to or in excess of 0.35 p.p.m., and those collected from water with combined available residual chlorine predominating and having 0.10 p.p.m. or less free available residual chlorine. The former group will be referred to as the free available

Table 1

Geometric Means of the Number of Bacteria on Agar per 1.0 ml., 35-37° C., 48 Hr. Incubation

Time (in minutes)	Geometric Mean of Number of Bacteria on Agar/1.0 ml., 35-37° C., 48 Hrs.	
	Pools with free available residual chlorination	Pools with combined available residual chlorination
0	3.8	42
0.5	7.4	148
1.0	11.2	315
1.5	12.9	453
2.0	13.2	445
2.5	14.3	539
3.0	22.1	672
4.0	16.5	630
5.0	14.2	634
10.0	7.9	304

Note: All swimmers entered water at 0 minutes and left at 5.0 minutes. No swimmers in water at 5-10.0 minutes.

residual chlorine group and the latter as the combined available residual chlorine group. Seven of the 12 sample series were classified as belonging to the free available residual chlorine group.

"The first measurement of the relative germicidal properties of free available residual chlorine as compared to combined available residual chlorine used the total agar plate count. A geometric mean of the number of bacteria growing on tryptone glucose extract agar at 35-37° C. for 48 hours for 1.0 ml. for each time interval during the sampling series for each of the two residual chlorine categories was determined (see table 1)."

"To measure the relative bactericidal properties of free available residual chlorine and combined available residual chlorine the results of analyses for coliform and streptococcal bacteria were compiled. . . . The tabulation of the results for coliform bacteria indicates that only 5 samples out of 168, or 3 per cent, showed the presence of coliform bacteria in any dilution in the water with free available residual chlorine while 84 samples out of 120, or 70 per cent, were positive for coliform bacteria in pools having combined available residual chlorine. When the chi square test is applied to these data a very highly significant result is obtained, which means that within the range of this study free available residual chlorine is more effective than combined available residual chlorine in swimming pools in killing coliform bacteria. The tabulation of the results for streptococcal bacteria indicates that 103 samples out of 168, or 61 per cent were positive for streptococci in swimming pool water with free available residual chlorine, and that 106 samples out of 120, or 88 per cent, contained streptococcal bacteria in the presence of combined available residual chlorine. The chi square test gives a highly significant value to this relationship, indicating that within the limits of this study free available residual chlorine is a more effective bactericide against streptococcal bacteria than combined available residual chlorine.

"If these same data are regrouped to measure the relative resistance of coliform and streptococcal bacteria to free and combined available residual chlorine, it is found that streptococci are more resistant to both free and combined available residual chlorine in the concentrations encountered in this study than coliform bacteria, but the greatest difference in resistance was observed in the samples collected from swimming pool water containing free available residual chlorine.

"Another demonstration of the resistance of streptococci and coliform bacteria to free available residual chlorine and combined available residual chlorine may be made by determining the per cent of samples having a streptococcal density greater than coliform, and vice versa. Pools practicing free residual chlorination show a definitely higher percentage of samples with a streptococcal index greater than coliform. This relationship cannot be shown for combined available residual chlorination practices, probably because the lethal concentration of combined available residual chlorine for coliform bacteria in swimming pool water was not reached in this study under the bathing loads encountered.

"From the above data, it is readily understandable why incongruous bacteriological results have been obtained from swimming pools having the same bathing loads and the same total residual chlorine content but with varying quantities of free available residual chlorine. Free available residual chlorine is the bactericide of choice

to obtain acceptable bacterial densities in swimming pools while in use and at the same time maintain a low concentration of total residual chlorine.

"This study failed to clarify the role of streptococci as indicators of pollution in swimming pool water, but has pointed out that streptococci are recovered readily in swimming pools when in use even in the presence of concentrations of free available chlorine that are bactericidal to coliform bacteria."

According to this study, the values of 0.4 to 0.6 p.p.m. of residual chlorine as recommended by the Joint Committee Report, if interpreted to mean free available residual chlorine, will produce bacteriological results that will comply with the Joint Committee Report's recommended standards for total number of bacteria and coliform bacteria in swimming pools when in use.

"The minimum value of 0.7 p.p.m. which has been suggested in the past for swimming pools using chloramine (combined available residual chlorine) treatment is insufficient to produce bacteriological results under conditions of this study which will meet the recommended standards of the Joint Committee Reports."

The Hypoglycemic Effect of Penicillin — Valdés Ruiz, M., Juanes González, A. and del Alamo Lorenzo, J. L.— *Medicina*, 18: 47 (January) 1950.

In 1945, a case of gas gangrene in a diabetic was reported in which penicillin treatment resulted in disappearance of the glycosuria during and after treatment, although insulin treatment had been discontinued; at the same time profuse sweating and weakness appeared which were attributed to hypoglycemia although they were not controlled by ingestion of carbohydrates. It was concluded that the toxins from the infectious focus had impaired the function of the pancreatic islands and that after elimination of their harmful effect the islands were capable of keeping the patient free of glycosuria. Observation was also made of a hypoglycemic effect of penicillin and an effect of penicillin on the carbohydrate metabolism was considered; experimentally a transitory diminution of the glycemia was seen in 4 normal and 3 diabetic individuals after penicillin injection, with a subsequent rise above the initial value. One writer observed a hypoglycemic effect of penicillin in a diabetic with a terminal hepatic neoplasm, a case of pneumonia followed by empyema and a case of *Streptococcus viridans* endocarditis. He considered the possibility that penicillin might have an intrinsic effect on the carbohydrates in connection with its bacteriostatic effect, or that its hypoglycemic effect may be unrelated to its therapeutic effect and be based on a toxic effect on the liver analogous to that of synthaline; the latter seems possible on the basis of the lesions observed in guinea pigs poisoned with penicillin.

The authors studied 5 diabetics who had no superimposed infectious process, or at least none which would be influenced by penicillin; 2 of the patients had pulmonary tuberculosis. Two patients had no special diet and no insulin treatment while the other 3 had an adequate diet and were under insulin treatment. In all patients the glycosuria was studied before, during and after penicillin treatment; the penicillin was given in a daily dose of 200,000 units, for three days, except in 1 case in which it was given for five days. The glycemia was studied by means of a tolerance test with 50 Gm. of glucose, immediately before and after the penicillin treatment. Neither glycosuria nor glycemia showed any appreciable influence of the penicillin, except for small oscillations.

On the basis of their results the authors do not consider the modifications of the carbohydrate metabolism by penicillin as constant, and they believe that penicillin has no hypoglycemic effect; the observations reported above would then be mere coincidences or the product of other multiple causes. The authors are inclined to agree that the penicillin probably has an effect on the inhibitory infectious focus and this view is supported by the fact that all but 1 of the patients reported above had infectious foci, while the sole exception concerned a patient with an extraordinarily malignant hepatic neoplasm. It is a well established fact that diabetes is aggravated by any inflammation or infection, although the mechanism of this phenomenon is unknown. Another showed experimentally that pleural inflammation

does not alter the glycemia of the normal animal while it produces marked and rapid hyperglycemia in the diabetic animal. A study of the local proteolysis in the area of inflammation by means of determination of the urea, nonprotein nitrogen and amino nitrogen of the exudate demonstrated a more intense proteolysis in the diabetic animal, and the increased protein catabolism in the inflamed area of the diabetic animal was accompanied by an increase of the sugar and lactic acid in the exudate. Both these substances and the local proteolysis diminished when the animal was treated with insulin. These experiments demonstrate that in the diabetic animal intense gluconeogenesis from deamination of the protein molecules takes place in the area of the inflammation. The changes in the blood of the animals parallel those observed in the inflammatory exudate, and the rise of the blood sugar in diabetics with an inflammatory process is attributable to absorption of sugar newly formed in the area of inflammation.

The suggestions of one writer that there is a toxic effect of the penicillin on the liver and a destructive effect on the carbohydrates do not seem logical to the authors in view of the chemical structure, characteristics and in vitro actions of penicillin and the results of liver function tests as reported by many authors; furthermore if a toxic effect with a hepatic lesion would be dealt with, the hypoglycemic effect would be more lasting and recovery would be less prompt.

The authors conclude that the hypoglycemic effect of penicillin is due to elimination of the anti-insulinic effects of infections and toxins.

Emergency Treatment of Apoplexy — DE TAKATS, GEZA AND GRAUPNER, G. W. — *Practitioner*, 164: 242 (March) 1950.

At the writers' hospital 121 patients with apoplexy were studied between 1940-1946. The writers found 15 cerebral emboli, 53 cerebral thromboses, and 53 cerebral haemorrhages.

"Cerebral Embolism.—Cerebral embolism was diagnosed in patients with sudden cerebrovascular insult, who had an obvious cardiac lesion for the source of the embolus, or who had had previous embolic episodes to the brain or elsewhere in the body, whose spinal fluid was clear and showed no elevation of pressure. The ages in this series of patients varied from 18 to 60, the average being 53 years. The blood pressure varied from 110/80 to 210/100 mm. Hg. Seven patients belonged to the hypertensive arteriosclerotic group, and 8 to the rheumatic group. Of the 6 patients with cerebral emboli based on rheumatic heart disease only 1 died, a 40 year old male with heart failure; of the remaining 9 patients having cerebral emboli as postcoronary complications and hypertensive cardiovascular disease, 5 died. . . . The prognosis is better in the rheumatic group.

"Cerebral Thrombosis.—Cerebral thrombosis, or more appropriately cerebral softening, shows areas of malacia or necrosis in the brain as a result of stenosis or hyalinization of arterioles, whereas an arterial thrombosis is seldom encountered. In this group of 53 patients, 9 died in the attack. A fall in blood pressure and the anoxia of the inevitable bronchopneumonia of the unconscious patient seemed to transform the silent or latent cerebral softening into the clinical entity of 'thrombosis,' or even death."

To make a diagnosis of encephalomalacia —not embolus and not haemorrhage—the writers postulate a patient afflicted with cardiovasculorenal disease, moderate hypertension, and an onset which is often gradual. "While loss of consciousness was present in approximately one half of the cases, it did not persist for many days. Increased intracranial pressure was not observed, the spinal fluid was clear, and if the pressure of the spinal fluid was elevated, it was part of the hypertensive encephalopathy. This group is really diagnosed by exclusion of embolism and haemorrhage from the causes of stroke.

"The average age of this group was 60.8 years. The average blood pressure need not be stressed, since the study of the charts revealed that readings were determined at various stages of the attack and are therefore meaningless. . . . Postoperative or postcoronary hemiplegias were noted to be accompanied by a prolonged and rapid fall in blood pressure. This was also true in some strokes occurring during

sleep. The onset was sudden in 25 and gradual in 28 of the patients.

"If the patient did not die of the attack or of complicating bronchopneumonia, recovery was slow, improvement being noted in 20, and no improvement in another 20 patients. Fatalities were recorded in 13 patients, all of them dying between the fifth and twenty-eighth day after the accident.

"Cerebral Haemorrhage. — Cerebral haemorrhage was diagnosed in 53 patients; of these 41 died within a few hours or days, a mortality of 77 per cent. The average age of this group was 58.9 years, ranging from 41 to 80 years. The average blood pressure was 213/120, with extremes of 300/150 to 120/70. Again it should be pointed out that the vascular insult itself may modify the blood pressure readings, but the tendency for the highest pressures among the three types of apoplexy is well defined in cases of haemorrhage. Only a few patients showed a gradual onset, but even in these a deepening coma was observed. A sudden fulminating onset was observed in 49 . . . . of the patients. The spinal fluid was clear in 30 per cent. Over two thirds of the patients had bloody spinal fluid and three fourths had bloody spinal fluid or increased spinal fluid pressure (over 160 mm. of water). In massive haemorrhage the outlook was poor, only 9 per cent improving; 14 per cent were unimproved, and 77 per cent died.

"Attention should be called to the fact that in nonfatal haemorrhage the spinal fluid may be free of blood in one third of the cases, and the pressure is not elevated in one fourth of the cases. On the other hand, in patients with cerebral softening the spinal fluid pressure was increased in 10 per cent of the cases, due to hypertension. A second spinal tap done four to five days after the original insult may reveal red cells, frank blood, or increased pressure in patients with a slow leak of their intracerebral haemorrhage in the ventricular system or to the surface of the brain.

"There may, of course, be other reasons for acute cerebral anoxia, such as a long-lasting nitrous oxide anaesthesia with insufficient oxygen supply, or a prolonged operation on an exsanguinated individual, on a blue baby, or on hypertensives used to higher pressure. With the advent of the long-lasting operations, with or without profound loss of blood, the involvement in cerebral circulation must be considered.

"Localization.—From the standpoint of localization it should be remembered that the majority of vascular accidents occur in the region of the internal capsule, from where the motor, the sensory, and visual phenomena originate. The lesion in the basal ganglions affects the extrapyramidal system and thus is responsible for the rigidity of the hemiplegic limb. The cortex itself may only be involved in collateral oedema and produce flaccidity. Flaccidity followed by spasticity means the disappearance of cerebral shock and is the expression of the actual organic damage."

"The internal capsule is supplied by the perforating branches of the middle cerebral artery, which has been compared to the bristles of a beard. These are the vessels most often involved in a cerebrovascular accident and, depending upon the extent of haemorrhage or softening, there will be contralateral hemiplegia, sensory changes, facial changes and sometimes ipsilateral involvement."

"Outline of Treatment.—The earlier treatment is begun the better are the chances for hastening restitution. A brief cardiovascular and neurological examination is done and the history is obtained from the relatives. The patient is immediately placed in an oxygen tent; this not only helps his anoxia but may indirectly aid his aortic depressor and carotid sinus reflexes. If signs of increased cerebrospinal pressure are dominant, a spinal tap is done and spinal pressure is measured. Frank blood indicates cerebral or subarachnoid haemorrhage. Marked hypertension with signs of increased venous pressure in the neck requires venesection, which is done slowly, not more than 300 ml. of blood being removed at one time. Unless coma is deepening and a terminal condition is obvious, and if massive haemorrhage can be reasonably excluded, a sympathetic block is performed with the patient in the reclining or semisitting position in his bed."

For diagnostic and therapeutic purposes the writers have generally preferred the

anterior approach to the sympathetic chain. "The method used is as follows:

"The patient's neck is slightly hyperextended by placing a small pillow under the shoulder blade of the same side; the head is turned away from the site of injection. With an applicator dipped in iodine, a line is drawn from the mastoid process to the clavicle, through the tips of the palpable transverse processes. A dermal wheal with 1 per cent procaine (without epinephrine) is placed over the tip of the seventh transverse process. A 4 inch (9 cm.) 22 gage needle is inserted through this wheal. It must shortly make contact with the tip of the transverse process, which is quite superficial. Then the needle slides along the superior border of the transverse process until it contacts the body of the sixth cervical vertebra. Aspiration is now made for air bubbles, for blood, and for spinal fluid; if this is negative, 10 ml. of 1 per cent procaine solution are injected, aspirating repeatedly during this procedure.

"A successful block must be followed within 10 to 15 minutes by a Horner syndrome, by a dilatation of the conjunctival vessels, by a dryness and increased warmth of the face and ear lobes on the injected side, and by a rise in temperature and dryness of the corresponding upper extremity. Unless a Horner syndrome develops, the injection must be regarded as faulty and should be repeated.

"This cervical injection is done on the side of the lesion; this is not immediately obvious when the patient is seen quite early, since he may be quadriplegic and have a flaccid paralysis, although either a facial involvement or a beginning sensory change may point to the site of involvement. Dilatation of the pupil is more frequent on the contralateral side. Loss of pupillary reaction is again more frequent in haemorrhage.

"If improvement is to follow cervical sympathetic block, it should be noticed within the next 10 minutes. The improvement may then continue, and should a relapse occur, the patient must be reinjected." The writers have not given these injections more often than once every 24 hours, but they might be given 8 or 12 hours apart if improvement is followed by signs of deterioration (table 1).

Table 1

Apoplexies: Criteria of Improvement Following Stellate Block

	Number of Patients
Regained consciousness	6
Regained speech	5
Improved speech	12
Motor improvement	8
Abolished flaccid paralysis	10
No improvement	9

"A total of 105 injections has been given to 50 patients." More than half of these patients received only one injection, since in the writers' early experience they were not sufficiently aware of the importance of reinjecting the patient if the first injection seemed useful. "Today, it is customary to inject the cervical sympathetics daily until no further improvement is noted. It also seems that bilateral sympathetic block is more effective, at least in the animal experiment, but only a few simultaneous injections have been made in this series."

At least in the big cities, the patient must actually be in the hospital for some other reason when the cerebrovascular accident occurs, so that the injection can be given immediately. "Of the 5 patients injected within the first hour, 1 was a visitor, 1 a blue baby who developed a hemiplegia during the exposure of the tetralogy of Fallot, 1 was in the hospital for coronary occlusion, and 2 had previous peripheral emboli and were fibrillating." Of the 25 patients injected within the first 24 hours, 18 improved; of the 20 injected within 24 to 48 hours, 3 improved and of the 5 injected after 48 hours none improved.

Pediatrics

Encephalopathy After Combined Diphtheria-Pertussis Inoculation. Report of a Case — ANDERSON, IAN M. AND MORRIS, DAVID — *Lancet*, 1: 537 (March 25) 1950.

"In the United States of America, where it is estimated that 2,500,000-3,000,000 children are vaccinated against whooping cough annually, transient, serious, and even fatal neurological complications have recently been described following the inoculations. In the case reported here the child developed signs of severe cerebral damage shortly after the first inoculation with combined diphtheria-pertussis antigens."

"Case Record.—A boy, born on June 6, 1946, was the second child of a twin delivery (uniovular). This was a first pregnancy, and delivery was spontaneous and rapid, the second stage lasting an hour. There was no evidence of compression of the skull, asphyxia, or distress. The child was normal in health and development until the age of 2 years 4 months, when he was admitted to hospital on October 3, 1948, because of a generalised convulsion. This passed off rapidly but left him with a transient right hemiplegia, from which he fully recovered in five hours, and he was discharged from the hospital next day. At the time of this illness 3 other children in the same house were suffering from mumps, and he was diagnosed as a case of mumps encephalitis. No investigations were carried out.

"On January 16, 1949, at the age of 2 years 7 months, the twins were immunised with combined diphtheria-pertussis antigens. One twin remained well, but the patient developed a generalised convulsion 36 hours later and was admitted to hospital.

"On admission, on January 18, he was comatose, and his temperature was subnormal but soon rose to 101.8° F. The coma deepened, and a few hours later there were further generalised convulsions. There was no neck rigidity or Kernig's sign. The pupils were small and equal, and there was a doubtful reaction to light. The fundi were normal. The conjunctival, abdominal, and cremasteric reflexes were absent, the deep reflexes were brisk, and there were bilateral extensor plantar responses. The heart and lungs were clinically normal. The cerebrospinal fluid (C.S.F.) contained 2 lymphocytes and 21 red cells per c.mm., protein 25 mg. per 100 ml. (globulin not increased); chlorides 720 mg. and sugar 18 mg. per 100 ml. (not collected in a fluoride tube). No organisms were found. The urine was acid and contained a trace of albumin, no sugar, some acetone, and chlorides 2 Gm. per litre. The convulsions were controlled with intramuscular sodium phenobarbitone 1 grain. Glucose in saline solution was given rectally.

"January 19: The child's clinical condition remained the same. His blood sugar was 156 mg. and blood urea 107 mg. per 100 ml.

"January 20: His temperature was normal. He was in a deep sleep and was roused with difficulty. He yawned frequently. The white cell count was 11,000 per c.mm. (polymorphs 51 per cent, lymphocytes 32 per cent, monocytes 14 per cent, eosinophils 1 per cent). Lumbar puncture was repeated; the C.S.F. was clear, under a pressure of 25 cm. of H_2O, and contained 4 cells per c.mm. (2 red cells, 1 lymphocyte, and 1 polymorph), protein 30 mg. per 100 ml. (no increase of globulin), chlorides 720 mg. and sugar 95 mg. per 100 ml.; blood urea 87 mg. and serum calcium 2 mg. per 100 ml.; alkali reserve 50 vols. CO_2 per cent. Wassermann reaction negative.

"January 21: A right hemiplegia had developed and speech was lost completely.

"August 5 (Age 3 Years 2 Months): Radiograms of the skull showed no abnormality. A lumbar encephalogram showed much dilatation of the left lateral ventricle." (The text was supported by 4 encephalograms showing left lateral ventricle much dilated.)

October 12: The text was supported by an electroencephalogram showing diminished electrical activity of the left cerebral hemisphere.

"State on Discharge (January 8, 1950, at the Age of 3 Years 7 Months): Some

speech had returned, and he had a vocabulary of about 10 words. He was progressing mentally, understood much of routine living, and was cooperative in the ward, though given to tantrums. He played with other children but with little sense of cooperation. The right arm and leg were still spastic, but the hemiplegia was diminishing, and he could walk without aid or support. A right homonymous hemianopia was present, but it was impossible to plot detailed visual fields."

Discussion.—Neurological complications are known to have followed the injection of pertussis antigen and combined diphtheria-pertussis antigens, but the writers have found no record of such complications following immunisation against diphtheria alone.

"Complications of pertussis vaccination are extremely rare, but the results are so serious that, until the prophylactic value of such vaccination is established beyond doubt, it may be desirable not to vaccinate a child in whom there is any suspicion of the stability of the central nervous system as shown by the personal or family history. If there is any untoward reaction to the first injection, no further injection should be given."

Encephalitis in Diphtheria—Dolgopol, Vera B. and Katz, Selig H.—*American Journal of Diseases of Children*, 79: 640 (April) 1950.

"Five cases of inflammatory damage to the central nervous system in diphtheria are presented."

"Case 1.—A white girl, 7 years old, had a sore throat on May 23, 1948. The next day she had fever and swelling on the right side of the neck. Two days later the swelling extended to the left side of the neck. On the third day of illness she was seen for the first time by a physician, who diagnosed her illness as diphtheria and ordered hospitalization. On her admission to . . . . hospital on May 26, she had a massive bull neck edema and an adherent yellow membrane on the tonsils and uvula. The patient was given 60,000 units of diphtheria antitoxin. The cultures showed *Corynebacterium diphtheriae*. The following day, the fourth of illness, the edema spread from the neck to involve the wall of the chest. The patient was pale and disoriented and later became dyspneic. She suddenly tried to stand up in bed but fell back with convulsions of the lower extremities; she became cyanotic and respirations ceased. (The child was vaccinated against smallpox on her admission to the hospital, 15 hours before death.)

"Observations at Necropsy: Brain. The brain weighed 1,300 Gm. and was soft, with flattened convolutions but little meningeal edema. The blood vessels of the white matter were congested. Microscopically, a number of heavy cuffs consisting of many rows of lymphocytes was present in the gray and white matter of one convolution of the right frontal lobe. The veins located between the infundibulum and the chiasm were surrounded by narrower cuffs. In the basal ganglions and midbrain the cuffs consisted of one or two rows of lymphocytes. A small number of fat-containing phagocytes was present between the lymphocytes in the perivascular infiltrates of the right frontal lobe. Two small glial nodules were seen in the basal ganglions. Some moderately severe degeneration of ganglion cells was observed in the nuclei of the third nerve, in the spinal nucleus of the fifth nerve and in the olives. The myelin around the cuffed blood vessels was intact.

"Changes in Other Organs. The following lesions were also seen: extensive pitting edema of the neck and chest; membranous tonsillitis and pharyngitis, with a piece of shrunken membrane in the right piriform fossa; congestion of the larynx and trachea, but with no membrane; purulent bronchitis; areas of bronchopneumonia; dilatation of the heart, with degeneration of occasional myocardial fibers, but no myocarditis; passive congestion of the liver; toxic splenitis, and finely granular degeneration of the renal tubular epithelium.

"The *C. diphtheriae* was found to be toxic. *C. diphtheriae* was not recovered on culture of the heart's blood.

"Case 2.—A Puerto Rican girl, 7 years old, was admitted to the hospital on November 22, 1947, the sixth day of untreated diphtheria, with typical bull neck edema and a temperature of 101 F. A heavy membrane was present on the tonsils and uvula. The pulse rate was 118 per minute, but the cardiac action was regular and the

liver was at the costal margin. Seventy-five thousand units of diphtheria antitoxin was given immediately on her admission, and penicillin therapy was begun. *C. diphtheriae* was recovered from the throat. The child showed some improvement during the following three days, but on November 25 her liver descended to 2 fingerbreadths below the costal margin, and she died suddenly in cardiac failure on the same day, the ninth of her illness.

"Observations at Necropsy: Brain. The brain weighed 1,340 Gm. and appeared moderately edematous and congested. On section the blood vessels of the white matter were injected, particularly in the region of the internal capsules. The basal ganglions were moderately congested. Microscopically, the subarachnoid space was seen to be greatly widened and the meningeal veins were engorged with blood. Collections of lymphocytes were observed in the walls of several veins in the white matter of the frontal and motor cortex, the island of Reil, the hippocampal convolution and the basal ganglions. The lymphocytic collections were rather small and often did not entirely surround the vessel. Some hyperchromatic cells were present in the cortex, basal ganglions and dentate nucleus. Moderately severe degenerative changes were seen in some cells of the reticular substance (eccentric nuclei in some cells; shrinkage and hyperchromatic staining in others). The myelin was intact. A few perivascular hemorrhages were present in the thalamus and external capsules.

"Changes in Other Organs. Other lesions present were: membranous tonsillitis; early myocarditis; moderate congestion of the liver and small collections of lymphocytes in some portal areas; hyaline droplet degeneration of some renal tubules, and lymphocytic collections around some blood vessels in the corticomedullary junction.

"Postmortem culture of the heart's blood yielded no *C. diphtheriae*.

"Case 3.—A white boy, 6 years old, was admitted to the hospital on December 9, 1931, the third day of diphtheria, with a swollen neck, epistaxis and dyspnea. The temperature was 101 F. In the following days he showed evidence of myocardial and renal failure and died on December 17, the tenth day of illness. (Although the original chart was not available at the time of this review, it must be assumed that this patient, in common with all patients with diphtheria admitted to this hospital, received adequate doses of antitoxin.)

"Observations at Necropsy: Brain. The brain was large and edematous, weighing 1,530 Gm. Microscopically, there was only a slight edema of the meninges, but a pronounced marginal edema of the brain was noted. A few small perivascular hemorrhages were present in the gray and white matter of the cortex, in the pons and in the medulla. Lymphocytic collections in the walls of several veins were seen at various levels in the medulla, especially around one tractus solitarius. A few degenerated ganglion cells were seen in the dorsal nucleus of the vagus nerve and in the nucleus of the tractus solitarius on the same side. Glial nodules were observed in the dorsal vestibular nucleus, in the nucleus ambiguus and around the tractus solitarius on the same side of the medulla and in the dorsal vestibular tract on the other side. There was no degeneration of myelin in the cerebrum, the medulla or the roots of the cranial nerves.

"Changes in Other Organs. The following lesions were also observed: generalized anasarca; membranous tonsillitis; myocarditis; congestion of the liver, with toxic changes in the parenchyma; effusion of protein into the Bowman capsules of the kidneys, with minimal tubular degeneration and a few casts, and resolving pneumonia.

"Toxic *C. diphtheriae* was cultured from the larynx at necropsy.

"Case 4.—A white boy, 1 year old, was admitted to . . . . hospital on December 5, 1946, with a vague history of 'a cold and cough' of two weeks' duration and of two days of some respiratory difficulty. No medical aid had been sought until the day of his admission, when the respiratory distress had become severe. The child was taken to another hospital, where *C. diphtheriae* was found on direct smear from the throat, and was referred to . . . . hospital. He had a crusted nasal discharge and a congested throat, but there was no exudate in the pharynx or larynx. However, pieces of membrane were removed by suction from the trachea. The child was given 50,000 units of diphtheria antitoxin, 50,000 units of penicillin intramuscularly and sulf-

adiazine orally, but he died four hours after his admission.

"Observations at Necropsy: Brain. The brain weighed 960 Gm. and was moderately edematous. The white matter was congested. Microscopically, the subarachnoid space was somewhat edematous and one area contained a small number of macrophages. One small perivascular hemorrhage was present in the medulla. A small perivascular cuff was observed in the white matter of the cerebellum and another in one nucleus ambiguus, and two glial nodules were present in both nuclei ambigui. Some ganglion cells in the nuclei ambigui and in the dorsal reticular nuclei were shrunken and hyperchromatic. There was a prominent homogenizing degeneration of the cells in the dentate nucleus. The myelin was intact.

"Changes in Other Organs. Other lesions observed were: membranous tonsillitis and tracheitis; confluent bronchopneumonia of the right lung; toxic splenitis with hemorrhages into the pulp, and slight toxic degenerative changes in the hepatic parenchyma and in the renal tubules. The heart was normal.

"The *C. diphtheriae* isolated from the tonsils and lungs was of a toxic mitis type. The postmortem culture of the heart's blood was sterile.

"Case 5.—The patient was a white man, 26 years old, a soldier recently returned from Europe, who was admitted to the hospital on January 31, 1946, the second day of nasal and faucial diphtheria. He was immediately given 60,000 units of antitoxin. During the first 11 days in the hospital he also received 2,500,000 units of penicillin. Nose and throat cultures showed *C. diphtheriae* of the toxic gravis type. The heart was normal on his admission and for the first week the electrocardiographic tracings revealed no abnormality, but from then on the picture was that of toxic myocarditis. Four weeks after his admission the patient displayed extreme mental depression. Several days later he began to complain of diplopia, nasal regurgitation with nasal speech and numbness of his fingers and feet. On the forty-fifth day of illness he had respiratory difficulty requiring use of suction, the Trendelenburg position and oxygen, and he died in respiratory failure.

"Observations at Necropsy: Brain. The brain weighed 1,600 Gm. The meningeal blood vessels were congested and the cerebral convolutions were flattened. Microscopically, there was a moderate cortical perivascular edema. Perivascular collections of lymphocytes, one cell thick, were present around a number of capillaries in the white matter of the frontal cortex. Several clusters of lymphocytes were observed in the interstices between adjacent small blood vessels of the basal ganglions and of the olives. No significant cellular changes were seen in the cerebral cortex, cerebellum or medulla, but there was some satellitosis in the motor cortex. More cellular damage was present in the thalamus, where large vacuoles were seen in several ganglion cells. No myelin damage was observed in the white matter of the brain or in the roots of the nerves arising from the medulla. The midbrain, unfortunately, had not been examined and no blocks of that tissue were available.

"Intercostal Muscles and Nerves. Hydropic and Zenker's degeneration was present in many muscle fibers. There was no inflammatory infiltration in the perineurium of the small nerve trunks, but the endoneurial fibers were coarse and collagenous, and some of the nerve fibers were devoid of myelin.

"Changes in Other Organs. Other observations were: severe, partly arrested, myocarditis with some fibrous replacement; bronchopneumonia (*Streptococcus hemolyticus*); moderate diffuse congestion of the liver; toxic splenitis with old and recent hemorrhages into the pulp; collections of lymphocytes beneath the renal capsule and around the corticomedullary blood vessels, and paleness of tonsils and larynx, but with cultures still yielding *C. diphtheriae*."

Histologic evidence of inflammation was present in all 5 cases that were classified as encephalitis. "Perivascular cuffing was present to a notable degree in 4 cases and minimal in 1 case. Glial nodules were seen in 3 cases, in 1 of them with evidence of neuronophagia. The medulla was affected in 3 cases with a history of 10 to 45 days of illness.

"Cellular degeneration was only moderately severe. . . . It usually did not go beyond central chromatolysis, with preservation of the Nissl substance on the

periphery of the cells and eccentric location of the nucleus." In the case of 45 days' duration no chromatolysis was seen in the medulla, but vacuolation of the cytoplasm was present in some cells of the thalamus. "The myelin was intact in the cerebrum, medulla, cerebellum and roots of the cranial nerves."

"The medulla was affected in cases of 10 or more days' duration.

"The central nervous system was probably damaged by direct action of circulating diphtheria toxin."

Ferrous Sulphate Poisoning. Its Incidence, Symptomatology, Treatment and Prevention — THOMSON, JAMES —*British Medical Journal*, 1: 645 (March 18) 1950.

"Six cases of ferrous sulphate poisoning are reported occurring in five years and five months in a town with a population of 182,000. . . . All took similar tablets containing ferrous sulphate exsic. 3 gr. (0.2 Gm.), copper sulphate 1/25 gr. (2.6 mg.), and manganese sulphate 1/25 gr. (tab. ferrous sulph. co., B.P.C.).

"Case 1.—On May 3, 1944, a 16 month old girl took 40 ferrous sulph. co. tablets from a paper packet and swallowed 39 of them at 10:30 A.M. She was given salt and water to drink and returned 13. Thus 26 were retained. She became hot and drowsy, and kept on coughing and vomiting. The vomit contained blood-stained material. On admission at 11.50 A.M. she was drowsy, pale, and still coughing and vomiting. The temperature was 96° F., pulse 140, and respiration 24. The pulse was of slightly diminished volume. The abdomen was slightly distended, but there was neither tenderness nor resistance on palpation. In the evening she was breathing heavily but was otherwise comfortable. No further vomiting occurred, but one loose stool containing mucus and dark blood was passed. At 7.30 A.M. on May 4 (21 hours after taking the tablets) her temperature rose suddenly, breathing became difficult, and the child became cyanosed. She appeared to choke on inspiration and died at once."

At postmortem examination intense inflammatory change in the gastric mucosa and a marked degree of necrosis and sloughing limited to the crests of the longitudinal rugae were found. "The necrosis extended down to muscle. In contrast to the stomach there were only a few patches of congestion in the upper jejunum. The intestine was otherwise healthy.

"Treatment: She received salt and water to drink before admission, and on admission gastric lavage with a sodium bicarbonate solution was carried out. Normal saline was left in the stomach, and 2 ½ gr. (0.16 Gm.) of bismuth carbonate was given four hourly, and sodium bicarbonate 15 gr. (1 Gm.) at 8 P.M. She was also given glucose and orange juice, and later diluted milk.

"This child died after retaining about 26 pills in spite of what, in view of subsequent investigations, seems to have been the correct treatment with bicarbonate solution to dilute the corrosive iron and also to reduce its solubility by altering it to the less irritant ferrous carbonate.

"Case 2.—On March 4, 1947, at about 9:30 A.M., a boy aged 2 swallowed about 10 tablets similar to those in case 1. Approximately half an hour later he began to vomit, and 2 tablets were returned whole. There was no haematemesis. His appearance became 'waxy,' but improved before he was admitted at 2.5 P.M. the same day. On admission he was flushed and drowsy, and there was neither abdominal tenderness nor abnormal resistance on palpation. A stool passed later in the day gave a positive guaiac reaction. Vomiting ceased by March 6 and the stool was normal by the ninth with no blood. On the thirteenth the guaiac test was again positive; no meat had been given. Further recovery was uneventful.

"Treatment: He was given ½ ounce (14 ml.) of mist. magnesium hydroxide on admission and bismuth bicarbonate 2 ½ gr. four hourly along with glucose and water, later changed to milk and subsequently to milk diet.

"Case 3.—On July 6, 1947, a girl aged 4 ½ years swallowed about 24 tablets. An hour later, according to her mother, she vomited about 20 of them. On admission she was slightly pale. Her abdomen was normal on palpation. She received 2 ½ gr. of bismuth carbonate four hourly, but never exhibited any symptoms of illness except the vomiting before admission. According to the history she returned 20

tablets in recognizable shape one hour after swallowing them."

Case 4.—On February 8, 1948, a girl aged 11 months was admitted under the writer's care.

"At 7.30 P.M., while playing with a box of these tablets prescribed for her mother, she swallowed an unknown quantity of them and became drowsy and vomited. On admission at 9:30 P.M. she was pale and drowsy; the abdomen was soft and not tender. She vomited altered and bright red blood until 10 P.M., when vomiting ceased. Next day she seemed well and played with her toys. She passed two tarry stools. But on the morning of the tenth she became cyanosed and had moist accompaniments at both bases. She died 39 hours after taking the pills.

"On postmortem examination extreme congestion of the mucous membrane was found; but the necrosis, though locally severe, was not so striking as in case 1. The small intestine showed a few areas of congestion less marked than in the stomach.

"Treatment: This consisted of gastric lavage with sodium bicarbonate in water, also bismuth bicarbonate 2 ½ gr. in mist. cretae four hourly.

"Case 5.—On July 14, 1949, a boy aged 19 months took some tablets off a shelf and was found eating them. He probably ate about 10. Before admission he was given syrup of figs and then salt and water, after which he vomited brown fluid several times. There was no red blood in his vomit. He then went to sleep, and was admitted 1 ½ hours after taking the tablets. A stool examined on the sixteenth gave positive reactions to Kastle-Meyer and benzidine tests for blood. Recovery was uneventful.

"Treatment: Gastric lavage with sodium bicarbonate produced clear fluid with streaks of blood-stained mucus in it. On the fourteenth dimercaprol, 0.5 ml., was given four hourly for a few doses, but was stopped on the fifteenth.

"Case 6.—On October 2, 1949, a boy aged 2 ½ years was discovered at 8 P.M. with his mouth full of tablets which had been supplied to his mother. The quantity he ate is not accurately known, but was probably between 10 and 20. He was given syrup of figs at home, and vomited at 8.15 P.M.; subsequently he vomited five more times. The first five vomits contained 'white bits and green stain.' The last vomit contained only 'water.' He complained of a sore stomach after swallowing the pills, and was drowsy at 9:30 P.M. He was admitted at 11 P.M. awake but sleepy. His abdomen was soft and not tender. Gastric lavage was carried out with saline, and ½ ounce (15 Gm.) of magnesium sulphate in solution was left in the stomach. On the third and fourth he passed two loose dark stools each day. The guaiac and Kastle-Meyer tests were negative. His further recovery was uneventful."

"The clinical picture of these cases is pallor at an early stage, followed by drowsiness, and vomiting early but ceasing after a few hours. Abdominal pain was noted in only 1 case, while none had abdominal tenderness or abnormal abdominal resistance. Haematemesis may be severe and early or not be clinically evident. Blood is probably present in the stools in most cases. . . . An important point is that whole tablets or fragments of them may persist in the stomach for at least one hour. Emesis in addition to lavage is therefore important for prompt elimination of any iron still in pill form."

The treatment given to case 1 seems to have been appropriate—namely, gastric lavage with an aqueous bicarbonate solution to convert as much as possible of the corrosive ferrous sulphate to the much less irritant ferrous carbonate and to dilute it. "Also to get rid of pills by emesis, which has been successfully done half an hour to one hour after ingestion; then to protect the mucosal lesions by bismuth. This seems to be the rational method of attempting to prevent the delayed sudden fatal collapse occurring after a deceptive period of improvement."

"It is abundantly clear that prevention of this accidental poisoning is important and urgent. The makers of 'fersolate' tablets have now added a warning: 'Excessive doses of iron can be dangerous. Do not leave these tablets within reach of young children, who may eat them as sweets with harmful results.' They also supply the tablets in a screw-topped container which would baffle the younger children. Welfare and antenatal clinics in particular should review their methods of issuing the useful ferrous sulphate tablets to adults. They should never be issued in paper packets or a carton with a loosely fitting lid."

Results of the Technic of Pinkus in Exsanguino-Transfusion of the Newborn — GAUTIER, P., THÉLIN, F. AND VOGT, A. — *Annales paediatrici*, 174: 128 (January-February) 1950.

The technic of Pinkus has been adopted at the Pediatric Clinic in the treatment of hemolytic disease of the newborn.

Briefly, Pinkus advised using the supraumbilical vein for the introduction of the catheter of Diamond. Above the umbilicus, this vein follows a course of 2 to 4 cm. in the abdominal wall outside the peritoneum and Pinkus has shown that this vein remains permeable for 15 days to 3 months after ligation of the cord.

The advantages of this route appear to be decisive and have permitted making four exsanguino-transfusions the results of which will be described later.

The technic of denuding the supraumbilical vein is very simple. The vessel is isolated under a local anesthetic by a transverse incision ¾ to 1 cm. long above the umbilicus. Under the subcutaneous cellular tissue and the transversalis fascia there is found a white cord 5 mm. wide which is easy to isolate and incise. The walls of the vein are sometimes collapsed, however, it is always easy to introduce a Diamond catheter of 3 to 4 mm. After the operation is terminated the vein is ligated and the skin is closed with a few sutures.

The supraumbilical route permits working under conditions of surgical sterility which is not the case when the umbilical cord itself is used. The route of access is easier than denudation of the saphenous vein which sometimes presents variations of anatomic arrangement and, especially, the vessel is much larger than the largest of the veins situated at the fold of the elbow. Finally, the operation is conducted under better conditions of security than puncture of the longitudinal sinus.

Before birth and in the hours which follow, the indications for exsanguino-transfusion are determined by prenatal serologic tests, which should be systematic, and also by the clinical and serologic examination of the infant (proof of incompatibility and proof of isoimmunization of the mother). The importance of Coombs' test (indirect search for incomplete antibodies) is of great merit. In the absence of clinical or hematologic signs, a positive Coombs test suffices as an indication for exsanguino-transfusion.

In the days which follow birth, it is more difficult to determine the indications; according to French authors in general, they are rather comprehensive and can be summarized by the empiric conclusion that an exsanguino-transfusion should be given in all cases of hemolytic disease of the newborn when it is not certain that they will become cured spontaneously or by a simple transfusion.

In the 4 cases treated by the method of Pinkus, the immediate results were excellent since before this method was used several cases of hemolytic disease of the newborn were partially transfused by other routes, double or single, and the patients died within 24 hours while with the method of Pinkus the 4 patients are still alive from one to five months after the operation.

There may be a rather profuse hemorrhage from the operative wound during the first few hours due to the presence of the heparinated blood used but this does not prevent cicatrization by first intention.

The weight curve shows a regular rise with artificial alimentation, sometimes with human milk, but never with maternal milk.

Finally, hematologic tests show a secondary anemia which appears regularly between the third and sixth weeks. This is probably due to the disappearance of the transfused red cells and a certain degree of sideration of the bone marrow. Theoretically, the antibodies of the mother have been removed during the exsanguino-transfusion (serum and red cells of the infant); this seems to indicate that the secondary anemia is not due to a persistent hemolysis, but this is not yet certain.

If the hemoglobin descends below 50 per cent, a transfusion of 30 to 50 cc. is made into the longitudinal sinus using blood from the donor who furnished the blood for the exsanguino-transfusion; however, theoretically blood from the same group as that of the infant can be used.

The prognosis of the operation by this method seems to be very favorable since all of the infants treated up to the present time have presented a perfectly normal psychomotor development. This indicates greater security for the future and for this

reason it was judged to be of value to speak about this method once more.

Case 1. Child of second pregnancy. Intense jaundice during the first hours. Petechiae due to hypoprothrombinemia. Marked anemia with 1,670,000 red cells and 40 per cent of hemoglobin. Severe erythroblastosis. Splenomegaly. Typical Rh.

Case 2. Child of fourth pregnancy. No previous complications. Intense jaundice during the first hours. Slight anemia without erythroblastosis. Typical Rh. This was a borderline case.

Case 3. Child of second pregnancy. Intense jaundice in a few hours. Splenomegaly. Anemia with moderate erythroblastosis. Typical Rh.

Case 4. Child of seventh pregnancy with four spontaneous miscarriages and one interruption at the fourth week, one premature stillborn infant at the sixth month. This infant was born at term. Grave jaundice after the sixth hour. Splenomegaly and grave progressive anemia with slight erythroblastosis. The father, mother and the infant were of group O and Rh+, but the mother had agglutinins against the subgroup "c" present in the infant.

Tick Paralysis. Report of a Case in Philadelphia — DAWSON, KATHERINE E., SHERMAN, ALFRED J. AND LABOCCETTA, A. C. — *American Journal of Diseases of Children*, 79: 491 (March) 1950.

"The sudden onset of an ascending type of flaccid paralysis, severe ataxia and asynergy, the dearth of abnormal laboratory findings and the rapid, complete recovery following the removal of the tick are typical of most cases of tick paralysis. All authors stress the importance of prompt diagnosis, since failure to remove the tick early in the course of the disease usually results in the progression of the ascending paralysis with subsequent bulbar involvement, respiratory paralysis and death within a matter of days or hours."

Since no cases have been reported from Pennsylvania, the following case of tick paralysis in Philadelphia is reported:

J. B., a white girl, 9 years of age, was admitted to hospital on July 26, 1948. "Two weeks prior to her admission she had an infection of the upper respiratory tract which lasted only a few days. Two days before her admission she complained of chilliness, but no frank chill occurred. About the same time paresthesias ('needles and pins' sensation) were noted in both the hands and the feet. The day before her admission she awakened to find that she was extremely weak and unable to stand or sit up. She complained of stiffness of the back and diplopia, and one episode of vomiting occurred.

"On physical examination her temperature was 99.6 F.; the pulse rate 110 and respirations 24 per minute. She was a well developed and fairly well nourished child who was acutely ill and quite lethargic. She was, however, fully oriented and aware of her surroundings. The hands were maintained in a clawed position. Her speech was thick and there was a nasal twang to her voice. The ocular fundi were not remarkable. The tympanic membranes were slightly dull and thickened; no exudate was noted. The pharynx was injected. The lungs were clear and the heart normal except for sinus tachycardia and a soft systolic murmur at the apex, which was not transmitted. Examination of the abdomen revealed no abnormalities. On neurologic examination there were palsy of the peripheral facial nerve on the left and questionable weakness of the soft palate on that side. A lateral nystagmus was present. There was generalized muscular weakness, more pronounced in the lower extremities. She was unable to stand, sit or even turn over in bed. All superficial and deep tendon reflexes were absent, and no pathologic reflexes were present. There was definite ataxia with dysmetria and asynergy. Position sense was lost in the fingers and toes, and there was questionable loss of vibratory sense in the lower extremities.

"A lumbar puncture performed on her admission revealed a clear, colorless fluid under normal pressure. The cell count showed 1 lymphocyte; chlorides were 630 mg., protein, 24 mg. and sugar, 42 mg., per hundred cubic centimeters. No organisms were seen on smear, and a culture was sterile. Serologic and colloidal gold reactions were negative. Blood studies revealed a hemoglobin concentration of 14.5 Gm., 4,850,000 red blood cells and 16,900

white blood cells, with 84 per cent neutrophils, 14 per cent lymphocytes and 2 per cent monocytes. No basophilic stippling was noted and there were no toxic granules in the white cells. The sedimentation rate (Wintrobe method) was 9 mm. per hour. Two blood cultures were sterile. Urinalysis showed a trace of albumin, occasional erythrocytes and rare hyaline casts. Determinations for lead and arsenic on a 24 hour specimen of urine gave negative results. An electrocardiogram and roentgenograms of the chest and skull were normal.

"The patient was treated symptomatically, and on the first day in the hospital (the third day of the disease) her temperature fell to normal. On the third day in the hospital the patient felt stronger subjectively, and her facial palsy seemed slightly improved; her position sense and vibratory sense were intact. The ataxia was less pronounced than formerly. On the morning of the fourth day in the hospital (six days after the onset of symptoms), while combing the patient's hair, a nurse discovered a large tick firmly implanted in the scalp over the left parietal region." The tick was removed in toto by gentle traction with forceps and was identified as *Dermacentor variabilis* Say.

"After removal of the tick, improvement was rapid and dramatic. Within 24 hours the patient's facial paralysis and ataxia had disappeared, all reflexes were present, and she was able to sit up without assistance. On standing, however, she complained of vertigo. On the sixth day of hospitalization she was allowed up in a chair and could walk without difficulty. She was discharged from the hospital, completely recovered, on the seventh day, August 2.

"The patient's course in the hospital was complicated when, on the fourth day, there was a slight elevation in temperature and a serosanguineous, foul-smelling discharge appeared in the right ear. On examination, the tympanic membrane was seen to be injected, but not bulging, and no perforations were observed. She was treated with sulfadiazine, 0.5 Gm. every four hours for two days, during which time the otitis cleared completely. Cultures of the discharge were sterile.

"After the discovery of the tick, the patient's mother volunteered the information that many dogs in the vicinity of her home harbored ticks and that ticks had been found on her own dog on several occasions. An investigation of the home environment . . . . did not substantiate this. Additional history was obtained of a trip to the farming area of Atco, New Jersey, seven days prior to the onset of symptoms. The common dog tick is indigenous in this district, so that, although the actual time and place of the tick infestation were not determined, there were several possible sources in the patient's environment.

"Two months after her discharge, a follow-up study of the patient showed a normal, healthy child who was going to school, eating well and gaining weight. She has had no recurrence of symptoms."

Successful Treatment of C. Diphtheriae Subacute Bacterial Endocarditis with Penicillin and Streptomycin — ALMKLOV, JOHN R. AND HANSEN, ARILD E. — *Pediatrics*, 5: 437 (March) 1950.

"Finding *C. diphtheriae* as the causative organism in subacute bacterial endocarditis is unusual. Only 17 cases have been reported and none has survived." The successful treatment of an 8 year old child with the combined use of penicillin and streptomycin warrants presentation of the case.

Case Report.—B. D., an 8 year old white female, entered the hospital. "Present illness started three weeks earlier when she developed an upper respiratory infection. Four days later she had a shaking chill followed by a high fever. Because the temperature remained elevated during the next three days the family physician prescribed both penicillin and sulfadiazine. At this time the patient complained of abdominal pain and had anorexia. Fever continued but the abdominal pain subsided. On the twelfth day of illness she complained of pain in her right heel. There was no heat, tenderness, swelling or limitation of motion of the affected joint. The pain shifted next to the right knee and then to the left knee. There was a weight loss of 2.25 Kg. during the three weeks preceding her admission to the hospital.

"Her past history is significant in that at 4 years of age she had tonsillitis followed by joint pains. A heart murmur was detected and with the assistance of electro-

cardiographic and roentgenologic examination her physician made the diagnosis of rheumatic heart disease. It is also pertinent that in several examinations prior to this illness, her physician had not reported the presence of a murmur. There was no history of rheumatic fever in the family. The patient was immunized for diphtheria when she was an infant, but the mother did not know whether the subsequent Schick test was positive or negative.

"Physical examination revealed a chronically ill, pale, listless child who appeared fairly well nourished. Blood pressure 90/60 mm. Hg., pulse 102/min., respiration 20/min., temperature 39.7° C. Nose and throat were clear. There were a few moist rales at the base of the right lung posteriorly. Left border of cardiac dulness was 2 cm. outside the midclavicular line. Apical impulse was in the sixth ICS. There was a loud, harsh murmur heard throughout systole, loudest at the apex. A faint diastolic murmur was also present at the apex. Rhythm was regular and the tones were of fair quality. The liver was palpated 3 cm. below the costal margin and was slightly tender. The spleen was not palpable. The patient complained of pain in the left knee but no objective evidence of disease was found on examination. There were no petechiae. The rest of the physical examination disclosed no abnormalities.

"Laboratory Examination: Hgb. 10 Gm./100 cc.; RBC, 2.3 million; WBC, 7.6 thousand with 75 per cent neutrophils; corrected ESR (Wintrobe) 28 mm. in one hour; antistreptolysin titre, 50 u./cc.; tuberculin test 1: 1,000 OT, negative; Schick test, negative; Kahn, negative; fasting blood glucose, 105 mg./100 cc.; and repeated urinalysis, negative except for albuminuria during febrile episodes.

"Bacteriologic studies of the nose and throat revealed alpha streptococci but were negative for *C. diphtheriae*. Blood culture on admission revealed a pure culture of *C. diphtheriae*. Two days later, the blood culture was again positive for the same organism. Because of the unusual nature of the bacteria, isolated from the blood stream, special studies were made. All the bacteriologic characteristics of *C. diphtheriae* were found and it was classified as an intermedius strain. The virulence test was positive when the organism was injected into guinea pigs.

"ECG taken three days after admission revealed a rate of 105/min.; P-R interval, 0.17 sec.; low T wave in lead I, and a negative T wave in lead IV F. Fluoroscopy of the heart demonstrated enlargement of the R and L ventricle. There also was a slight enlargement of the L auricle."

Course in Hospital: "Because of the positive blood culture on the third day of admission, penicillin, 200,000 units every three hours intramuscularly were exhibited. The next day the patient complained of pain in her right elbow but examination of the joint was not remarkable. The joint pain did not respond to salicylate therapy. Caronamide was given for a period of 11 days starting 4 days later, the dose being 1.4 Gm. every 4 hours for a total of 92.4 Gm. On the fourteenth day of admission the patient complained of severe pain in her right chest and developed a rise in temperature to 40° C. Venous pressure was 18.5 cm. of saline. Roentgenographic examination of the chest revealed evidence of an infarction in the right lower lobe.

"One month after admission the patient developed a temperature of 40.6° C. and became stuporous. Her condition was extremely critical. Sensitivity tests on the organism which were carried on during this interval revealed: penicillin sensitivity, 0.05 u./ml.; streptomycin, 3.0 u./ml.; and Na-sulfadiazine, 5.0 mg./100 ml. Because the patient had failed to respond to penicillin alone and because the organism was fairly sensitive to streptomycin, it was decided to employ this drug as well as the penicillin. Streptomycin was given intramuscularly, 0.5 Gm. every six hours. Improvement was dramatic following exhibition of the streptomycin. Nine days later the dose was reduced to one half and the drug was discontinued after 23 Gm. had been given during a 16 day period. The patient remained essentially afebrile but penicillin was continued. A total of 75,200,000 units was given parenterally during a three month period. The intramuscular penicillin maintained a blood level of 1.5 u./ml. In addition to the penicillin therapy, because of marked cardiac failure, the patient was on a low salt diet. Intranasal oxygen was administered for 45 days. Supportive therapy also included xanthine and mercurial diuretics and seven blood transfusions.

"The patient continued to improve and remained afebrile. Her course was uneventful except that three months after admission she developed an abscess of the buttocks. This influenced the staff physician to prescribe oral penicillin. The dosage of oral penicillin employed was 800,000 u./day and was given for a two month period for a total of 55,200,000 units. This dose sustained a blood level of 0.6 u./ml. The abscess was incised and drained. The culture of the purulent material was sterile. She was discharged from the hospital six weeks later with the recommendation that oral penicillin be continued. There had been 20 consecutive negative blood cultures.

"Second Hospital Admission: Two weeks after discharge, because of the return of the inflammation in her buttocks she was readmitted to the hospital. Physical examination revealed an alert, active, happy child. A harsh systolic murmur over the entire precordium, loudest at the apex, as well as a faint apical diastolic murmur were readily elicited. The left border of cardiac dulness was 1 cm. outside the left midclavicular line. ECG revealed a rate of 105/min.; P-R interval, 0.16 sec., and a diphasic QRS in leads I, II, and III. Roentgenographic examination of the heart showed distinct reduction in size but there was a moderate R ventricular enlargement, slight L auricular enlargement, and some L ventricular enlargement. There was a prominent pulmonary conus. When the patient was discharged on the eighth day, the induration in the buttocks had resolved. The oral penicillin was stopped and the patient was placed on sulfadiazine 0.5 Gm. twice a day as a prophylactic measure for the prevention of a possible recurrence of rheumatic fever.

"Follow-Up Study: Since her discharge from the hospital, she has continued to remain well and has gained 2.5 Kg. She has been examined at weekly intervals for six weeks in the outpatient clinic and has had normal sedimentation rate."

"In spite of the daily administration of 1.2 million units of penicillin the patient's course in the hospital continued to be stormy. She was in variable degrees of cardiac failure. Even after four weeks of penicillin therapy the patient went into marked failure; her temperature rose to 40.6° C. and she became comatosed. No precedence for the use of streptomycin in such a condition could be found, but with a sensitivity of 3 u./ml., it was felt justifiable to use this antibiotic. The response to the added streptomycin was dramatic."

In view of the marked clinical response noted in this patient, the animal tests that have been performed and in vitro sensitivity tests, it would seem advisable to treat future cases of subacute bacterial endocarditis due to *C. diphtheriae* with a combination of large doses of penicillin and streptomycin as soon as a positive blood culture is obtained. "The combination of the two antibiotics would tend to reduce the possibility of the organism becoming drug resistant. Of course in vitro sensitivity test should be done on the organism as soon as it is isolated so the clinician may be able to ascertain the blood level necessary to combat the infectious agent."

Kerosene Intoxication — Reed, Edsel S., Leikin, Sanford and Kerman, Herbert D. — *American Journal of Diseases of Children*, 79: 623 (April) 1950.

Kerosene is frequently left carelessly about the house in open cans, bottles and other containers in reach of children who may find them and attempt to drink the contents.

"Kerosene ingestion may be followed by (1) acute toxicity with depression, (2) severe pneumonia with fever or (3) severe pneumonia with degenerative changes in the liver, kidneys, lungs and heart."

Twenty-five cases of kerosene ingestion were studied. "The patients studied ranged in age from 10 to 36 months, with an average age of 16 months. It was difficult to obtain an accurate history of the amount of kerosene ingested, and in 14 children the amount was unknown. Amounts varying from 1 teaspoonful to 1 cup (5 to 236 cc.) were said to have been ingested by the 11 remaining children."

"Irritation of the respiratory tract, the commonest finding, was manifested by coughing, gasping, choking or strangling. This was observed in 14 of the children. Vomiting was a prominent early symptom and occurred in 12 patients. Lethargy was observed in 8 children. Abdominal pain

and convulsions were observed in 1 patient.

"On examination the patients frequently showed evidence of both irritation of the respiratory tract and toxicity. The rapid, grunting type of respiration was common. Eight patients were found to have rales. The rales in 7 of the patients were described as coarse and bubbling in type, while 1 patient had fine, moist rales. These 8 patients had elevated temperatures and were considered clinically to have pneumonia. Cyanosis was present on admission in 2 of the patients.

"White blood cell counts were done on 20 patients and ranged from 6,450 to 35,200 cells per cu. mm. Leukocytosis (a cell count of 10,000 or higher) was found in 13 patients. This appeared to be due to an increase in all cellular elements. The red blood cell counts were not affected. Urinalyses showed the presence of albumin in 8 cases, varying from a trace to a 1 plus reaction. Sugar was found in 3 instances; all reactions were plus or under, while acetone (1 and 2 plus) was observed twice."

"Antibiotics, penicillin or sulfonamide preparations, separately or combined, were used in the therapy on 23 patients. The stomach was emptied either by involuntary vomiting or by gastric lavage in 16 of the children. Oxygen administration was considered necessary in 3 patients.

"The temperature was elevated in 80 per cent of the patients, and rectal temperatures ranged from 98 to 104 F., the average length of fever being 2.65 days. The average duration of the stay in the hospital was 7.52 days and varied from 2 to 27 days. Several of these patients were severely ill, but no fatalities occurred."

"Twenty-two of the 25 patients were studied roentgenologically. These were unselected. Roentgenograms were made of 16 patients within 24 hours of admission, while those for the remaining 6 patients were made between two and five days after admission. Of the 22 patients studied roentgenographically, 19 showed definite evidence of pulmonary changes.

"The criteria for diagnosis of pulmonary abnormalities consisted in the finding of definite areas of increased density in the pulmonary fields. Prominence of the bronchovascular markings was not considered as evidence of involvement unless associated with areas of parenchymal density.

"The roentgenologic appearance varied considerably in the individual patients. The findings ranged from a small patchy density in the right cardiophrenic angle in 1 child to large confluent mottled densities in another. These latter densities extended out from the hilar areas to involve the outer one third of the pulmonary fields and were most pronounced in the right midpulmonary and lower pulmonary fields.

"The pulmonary changes were seen oftenest bilaterally and were usually most pronounced in the base of the right lung. The changes were thought to be similar to those seen in pulmonary hyperemia or edema rather than pneumonitis. In 2 patients fluid was observed; in 1 the fluid was observed bilaterally, and in the other only in the left pleural cavity.

"The changes observed developed rapidly after the ingestion of kerosene and were usually resolved in approximately two weeks."

Because of the known fact that kerosene in contact with body tissues may result in fibrosis, the writers felt that a survey of the children who had previously ingested kerosene was indicated in an attempt to determine whether there was any residual pulmonary fibrosis or damage.

"Nineteen of the 22 patients examined had roentgenologic evidence of pulmonary abnormalities following the ingestion of kerosene. Thirteen of these 22 patients were available for follow-up studies. The follow-up examinations were performed six months to four years after the ingestion of the oil, the average being 19.5 months. The patients' parents were questioned closely about any pulmonary disorders since discharge, special attention being directed to the frequency of colds and chronic coughs. The children were also examined, and each had a roentgenogram of the chest. The histories were essentially normal for all except 2 children, 1 of whom gave the history of failure to gain weight in the past three months. The other child had frequent summer colds which 'he couldn't seem to get rid of.' The physical examinations gave normal results with 1 exception: One child had a systolic aortic murmur which was presumed to be functional and not related to the ingestion of kerosene.

"Roentgenograms revealed no evidence of active pulmonary or cardiac abnormality in any of the patients. Two children showed increased bronchovascular markings, with no definite evidence of fibrosis. There was no evidence obtained that kerosene pneumonitis leaves residual damage to the respiratory system."

Rocky Mountain Spotted Fever Treated with Chloramphenicol and Aureomycin — REILLY, WILLIAM A. AND EARLE, A. M. — *Journal of Pediatrics*, 36: 306 (March) 1950.

Rocky Mountain spotted fever (R.M.S.F.) is a self limited disease with an incubation period of 3 to 14 days, an abrupt onset in severe cases with a sudden rise in temperature, moderate to severe headache, neurological manifestations, and generalized aching and pain in back, neck, and extremities. "Vomiting may or may not be present. In milder cases the onset is more gradual. The characteristic rash of R.M.S.F. appears on the second to sixth day and may appear within 24 hours. The rash usually appears on the extremities first, but may appear on the trunk. . . . The febrile period lasts from two to three weeks and the temperature falls by lysis by the end of the third week."

A summary of 6 cases of rickettsial diseases diagnosed clinically as R.M.S.F. are presented.

"The differential diagnosis of rickettsial diseases at times is difficult; this is especially so between epidemic typhus fever and R.M.S.F. However, with a detailed history and minute observation of the patient it is relatively easier." All patients gave a definite history of tick bite and came from a part of the country where R.M.S.F. is known to be present. "The onset of the disease was within the range of the incubation period of 3 to 14 days. All had negative stool, blood, and urine cultures for typhoid and negative agglutinations for tularemia, typhoid, paratyphoid, and brucellosis, except 1 patient who was known to have received typhoid injections one year prior to onset of present illness and whose agglutination for typhoid H was 1:80 on the third day of illness. The rash, in all cases, appeared from the second to sixth day; the lesions were maculopapular, either bright or dark red, and in all except 1 patient acquired a petechial character. The spleens were palpable in all cases and 5 patients had palpable livers; however, none showed clinical jaundice. There was some degree of mental involvement from dulness, stupor, and coma to restlessness, insomnia, delirium, muscular rigidity, and tremor in all of the patients.

"Four patients out of the 6 had positive agglutination for ox 19." Although 1 case had negative agglutinations for ox 19 on two occasions, the authors felt that clinically this was R.M.S.F. In 1 case the first agglutination was done on the third day of the disease and the patient was signed out by his father before a repeat could be obtained.

In 4 cases treated with Chloromycetin, the drug was started on the sixth to eighth day of disease and continued for six to eight days. "The temperature returned to normal in 48 to 72 hours after starting Chloromycetin in 3 patients and in 1 patient the temperature fell to 101° F. in 72 hours but remained elevated for the next 48 hours, after which it returned to normal. The dosage of Chloromycetin was 25 to 50 mg. per Kg. in 24 hours. In the 2 patients treated with aureomycin, 1 patient was treated at home by a local physician and was given 50 mg. of aureomycin five times a day for two days. The temperature returned to normal and the rash faded. The patient was admitted to a hospital three days later, and at this time he had no elevation of temperature or rash. He was observed without therapy for 10 days when he had a sudden rise in temperature and a rash typical of R.M.S.F. reappeared. Aureomycin therapy was reinstituted, the temperature subsided after 24 hours, and the rash faded. The relapse was possibly due to too small a dosage of the drug initially." One case also treated with aureomycin, was given an initial oral dose of 750 mg. by stomach tube and two subsequent doses of 250 mg. at four hour intervals. "After this, the patient was given 60 mg. every four hours intramuscularly for seven days. There were no untoward reactions to either Chloromycetin or aureomycin.

"In all cases the temperature ranged from 104° to 106° until institution of therapy, at which time the temperature began to decrease and the rash faded."

The Present State of the Treatment of Tuberculous Meningitis and Its Results in the Children's Hospital of Zürich — Rossi, Ettore — *Helvetica paediatrica acta*, 5: 27 (March) 1950.

Streptomycin treatment of tuberculous meningitis was started in the Children's Hospital almost three years ago. The material may be divided into three groups; namely, that in which a high dosage was used, that in which a low dosage was used for short periods of time with long intervals, and that in which a low dosage was used over prolonged periods of time.

A total of 46 cases was treated, but 3 cases are excluded from the statistical evaluation as observation has been continued for less than six months. The first group included 7 children, all of whom died; the second group included 7 children, with 5 deaths. The results were much more encouraging in the third group; of the 29 patients in this group 18 were cured or markedly improved. Even children admitted in a moribund condition were included and 4 of them died within a few days after institution of treatment; the condition on admission is not a contraindication to institution of treatment and a few children who were moribund on admission could be cured completely.

An analysis of the results shows that most failures of streptomycin treatment involve either infants or children who were admitted too late; early diagnosis is therefore a prerequisite for successful treatment. The prognosis is much poorer in infants than in older children.

For more than a year 10 of the 20 patients who are still alive have been under observation and the other 10 for more than six months. Seven of these children show normal clinical findings and a normal spinal fluid, 5 show clinical cure but with a still positive colloidal gold reaction, 5 show cure with defects and normal spinal fluid findings, and 3 show clinical defects and residual pathologic spinal fluid findings.

Of the children with defects that are cured 4 show a more or less marked ataxia which however is demonstrable only on very accurate examination except in 1 case, 2 show a spastic paresis, 1 of them with a psychotic syndrome, 1 shows a lack of inhibition, and 1 shows a classical lesion of transverse section; in this case a laminectomy was carried out and revealed a tuberculous myomalacic focus with tuberculous arachnoidosis at the level of the sixth and seventh dorsal segments. Because of a rapidly developing block, intraspinal streptomycin treatment had to be discontinued too early in this case and the tuberculous focus below the block continued to develop. Exclusively intramuscular treatment must be considered to have been insufficient in this case. In another case a block developed because of too prolonged intraspinal treatment; treatment was continued with suboccipital injections and within six months the block disappeared spontaneously.

At present the author uses streptomycin intraspinally during the first two weeks in a dosage of 1 to 2 mg. per Kg. body weight daily, once or twice daily, alternately suboccipitally and intraspinally; during subsequent weeks the dosage is reduced to 1 mg. with only one puncture daily, depending on severity and course of the individual case. If the condition improves, from the second month on, the same dosage is continued with three injections weekly, and from the third month on, with two injections weekly; the latter are continued until the spinal fluid is normalized. The streptomycin is used in a solution containing 10 mg. per cc., at body temperature, and the suboccipital dosage is half the intraspinal one.

The author stresses that a protein concentration in the spinal fluid exceeding that of the suboccipital fluid by more than 10 per cent is considered as first sign of beginning blockage and as indication to continue with suboccipital punctures exclusively. Surgical procedures like introduction of thin catheters into subdural space and ventricle did not have to be resorted to, but reports seem to indicate that by means of them some infants can be saved who otherwise would have died. Determination of the streptomycin index between spinal and suboccipital fluid affords an even earlier diagnosis of beginning blockage. Intramuscularly the author gives 30 to 40 mg. per Kg. body weight daily during the first month, and then reduces the dosage to 20 to 30 mg., depending on the course of the disease. Intramuscular treatment is continued without intermis-

sions until complete normalization of the spinal fluid, but the daily total dose only very rarely exceeds 500 mg.

The author stresses the value of supportive treatment. Animal experiments have shown results which induced him to discontinue the use of sulfones. However, paraamino salicylic acid has been used systematically, in a dosage of 0.3 to 0.5 Gm. per Kg. body weight daily, divided into six doses; in order to avoid side effects like anorexia and vomiting, the drug was omitted for one to two days at intervals of three to four days. Based on reports from French writers the author dared to use paraamino salicylic acid exclusively for three to four weeks in 2 cases, with daily checks on the spinal fluid. These children had not had any other treatment before. According to the method of the French authors, 30 Gm. of the drug were given daily in an intravenous drip infusion and 10 cc. of a 5 per cent solution were given daily intraspinally. The number of cells and glucose concentration of the spinal fluid improved strikingly, the temperature became normal, and the general condition was highly satisfactory in the first case, while the protein concentration rose slowly. Suddenly on the thirty-second day a severe clinical picture with loss of consciousness and collapse supervened and the spinal fluid showed the classical signs of Froin's syndrome. Streptomycin treatment was then instituted and proved successful; the block persisted but clinical cure was complete. In the second case the transverse lesion developed. These 2 cases proved the efficacy of paraamino salicylic acid but the author concludes that intraspinal administration of this drug should be avoided absolutely, at least in the dosage suggested by the French authors as it leads with certainty to adhesions and is extremely painful. Furthermore technical problems have to be considered with respect to the intravenous drip infusion. Exposure and ligation of the vein leads to dangerous thrombosis within a few hours or days, while this difficulty can be avoided by introduction of very fine cannulas into the circulating venous blood so that rapid drainage of the drug and frequent change of veins are afforded; according to one writer these side effects can be avoided by buffering the solution to a p_H of 7.35.

In order to prevent the rather frequent side effects of anorexia and vomiting, the drug may be used in form of capsules and therapeutically satisfactory blood and spinal fluid levels can be achieved in this manner. In seriously ill and stuporous children a satisfactory level can be achieved with rectal administration of the drug. The granulated form of the drug is particularly indicated in infants and results in a high and protracted blood concentration so that only four administrations daily are required.

The author finally stresses the need for strict clinical control; all children with tuberculous meningitis are kept in the hospital for at least a year, even when the course is highly favorable, and subsequently most of them are sent to Davos for several months, regular checks on the spinal fluid findings being continued there. No child should be discharged before 18 months have passed, even when the course seems highly favorable. The treatment of tuberculous meningitis with streptomycin in low dosage over a prolonged period of time in combination with paraamino salicylic acid denotes a considerable progress and permits a certain optimism.

Symposium Section

Helping the Child Grow Up

Very few days pass in recent years without the appearance of a news story on juvenile delinquency. Moreover, there can be no question but that ample justification exists for printing such stories. Rarely does a day pass that something does not come over the teletype concerning a murder or some other major crime committed by a "teenager." Often it tells about the mass murder of entire families followed by the suicide of the young perpetrator of the crime. We read about murders with firearms, hanging, burning at the stake and less serious episodes among very young children at play. Small wonder that distraught parents frantically try to find out why such things happen with increasing frequency. Of course, we could go on from here and write many pages offering reasons. Most of them would be logical and beyond controversy but they would be nothing more than repetition of what has been written before and what has long been accepted by people of intelligence. The less intelligent, the constitutionally inferior and those whose mentality has been impaired by alcohol, barbiturates or inability to adjust themselves to the unparalleled confusion of a world in trouble, will probably continue to beat infants and physically and mentally crippled children to death in order to discipline them for crying for legitimate causes or failure to eat poorly prepared or unpalatable food.

It must never be forgotten that when a newly born gives its first cry and initiates that marvelous sequence of physiologic events by which the functions of respiration and circulation are established so that it can be on its own, its mentality likewise starts at zero. The moment it is placed to its mother's breast, as all babies can and should be, or is given a bottle of warm milk, the little mind begins to function. From then on its mental and physical destiny is in the hands of the parents. Upon how they meet this obligation will determine, for the most part, the whole future of the little individual. At no time in the history of this world has this obligation been more important and at the same time more difficult to fulfill. This is because the parents of today have more factors to overcome than those of more tranquil periods when the tempo of living was not so frightening. Nevertheless, conditions of today must be accepted and ways must be devised to overcome the handicap which they may create. In the foreseeable future no one need cherish any delusion that there will be any change in the movies, the radio crime programs, gangster glorification, the ghastly and gruesome pictures in the pictorial magazines or the detailed reporting of sex crimes or horrifying and repulsive murders, the weird and sensuous music and, lest we forget, the profane plays of the legitimate stage, until they cease to pay off in the untold dollars that they do at present. There is no use complaining about the clatter of machine guns or the constant shooting by the cowboys in the neighborhood movie as long as the demand for them exists. After all some of the freedoms are involved and in these precarious times there is danger of being subpoenaed to show cause why you should not be investigated as a communist if you write too much or talk too long and loud at a PTA meeting or a luncheon club. Besides it has all been discussed before and cannot be used as an alibi for failure to provide guidance for young children.

Instead these conditions must be accepted as a challenge to provide more careful piloting for the child who looks to his elders for leadership. The very existence of these conditions emphasizes that it needs this aid more than ever before. Children must receive more help and guidance better to prepare them for the impact of these sinister distractions. So, we will leave these unpleasant reasons for better child guidance for one of the most refreshing and

feasible discussions on helping the child to grow up that has come to our attention.

This is an understandable and common sense presentation of a subject which has so often been made so complicated for parents that they have frequently given up in despair and turned to less authoritative sources for information which most of them are eager to obtain. It was presented before the parents and teachers of the Preparatory Division of Juilliard School of Music in New York City on April 28, 1949, and it was published this year in *The Connecticut State Medical Journal* [14:111 (February) 1950] which is acknowledged as the source of the article.

It is called "*An Introduction to Child Guidance*" and its title is appropriately "*Helping the Child Grow Up.*" The author is Dr. Franklin S. DuBois, who is Associate Medical Director of the Silver Hill Foundation institution for the treatment of psychoneurosis at New Canaan, Connecticut. We were so impressed with this clear presentation that we felt this section could be put to no better use than to reprint Dr. DuBois' article in full instead of abstracting in accord with the usual procedure. We feel that it should receive wider circulation because if mothers followed its plain directions they could then throw away the "rigid book of rules." So without further comment and without quotation marks we acknowledge that what follows is wholly Dr. DuBois'.

* * *

INTRODUCTION

Much has been written and even more has been said by physicians, psychologists and educators in efforts to help parents guide their children in the process of growing up. Because of the wealth of material presented, even the most conscientious and thoughtful parent often gets lost in a maze of complex and sometimes obscure theories. Thus annoyed, he may retreat into a hostile attitude towards all methods of child guidance or, conversely, adhere tenaciously to a rigid book of rules. The beneficiary of these equally unfortunate attitudes, the offspring, reacts in kind and may become either an uncontrolled menace in the community or an adolescent burdened with timidity. How can these pitfalls be avoided? How can we provide our children with good techniques for assuming places in society as well equipped human beings who can stand on their own two feet in every sphere of activity? The physician, to whom parents ultimately turn, must penetrate the haze and offer definite advice based on a sound knowledge of the characteristics that distinguish a child's personality, an appreciation of the ultimate goals of the child, and an understanding of the attitudes of the parent that harm or help the child. It is these principles of good parenthood that I should like to consider with you.

CHARACTERISTICS THAT DISTINGUISH THE CHILD'S PERSONALITY

One must always remember that in dealing with a child, he is dealing with a child and not with an adult. This truism means little unless one comprehends the more conspicuous differences between the personality of the child and that of the adult.[1]

First of all, the child is pliant and flexible. Human behavior, in most of its aspects, depends upon habit and definitive habitual reactions have not yet been established in the growing child. The word habit is often loosely used but in a formal psychological sense it is an acquired physical and/or mental process of repetitive and ultimately automatic action. The infant is not born with habits, he must learn them. This fact more than anything else offers hope for the prevention of difficulties in adjustment and for the establishment of wholesome attitudes of mind and methods of action. Fortunately the child is not handicapped by rigid, well grooved patterns of response, but is malleable, tractable and open to suggestion, much as a green shoot can be bent to the gardener's will. Since habit is a repetitive process, it is obvious that establishment of good habits is desirable. And, further, since habits ultimately are unconscious methods of behavior, good habits of thought and action simplify life. Wise decisions are made automatically without conscious thought, and the intelligence is thus freed for use in those situations which cannot be solved by habit.

Because the child is pliant and flexible, he is infinitely more susceptible to environ-

ment than is the adult. Too often the anxious and unknowing parent is prone to ascribe his child's difficulties to constitutional factors, as exemplified by such statements as "he is a chip off the old block," or "he is just like his grandfather," or "blood will tell." These cliches are smoke screens for the more probable fact that the child mirrors in action either his father or mother. This parent, by his behavior, paves the way for imitation, a much more forceful influence in the child's life than the obscure and little understood chromosomes. In fact, it is safe to assume that nothing unusual or abnormal in the child's conduct should be ascribed to innate causes until the environment and personal situation have been studied meticulously and corrective measures instituted where needed. And even then, should the problem continue, one cannot be sure that inherited forces are at work. As Thom has so aptly stated "The great majority of children with undesirable habits, personality deviations, and delinquent trends are not the product of an irreparable past, over which there is no control. They are largely the results of the environment in which they have been reared; and the dominating feature of this environment is always the parent."[2] The father and mother must never forget that it is their relationship with the child that is of prime importance for the shaping of character. The factors of imitation and suggestion are of maximal significance. Parents can help the child most by teaching him, by example, the techniques of meeting each problem as it arises, in a way that is appropriate to the child at his stage of growth.

In addition to his plasticity and susceptibility to environment, the child differs from the adult in his profound self centeredness. He is egoistic in the extreme. At birth the world is his and the action of everything and every person about him is interpreted purely in terms of self. The process of growing up is, in effect, the adjustment of this tremendous egoistic drive to the restrictions of society. This idea of self includes self assertion, self importance and the need for affection and praise. These hold full sway in infancy, but as the child matures they are frustrated by the requirements of environment. Nevertheless, these inherent personality demands must have outlets—and outlets will be found. The wise parent directs these urges into legitimate channels before they spontaneously find illegitimate egress, and thus helps his child develop the adequate self esteem, independence and initiative essential for successful later years. Thoughtful parents make a child less demanding and less self centered by giving him adequate self satisfaction at each age level. Every child needs to feel that he is important, and on suitable occasions his importance should be emphasized. His birthday, for example, is unique in family annals; on that day he has first position in his group. He, in turn, yields precedence to parents, brothers, sisters and friends on their birthdays. His ego is satisfied. He has had his turn and enters with appreciation into a realization of how much pleasure the same treatment affords others. Even in giving birthday presents to others, he may justifiably achieve a sense of importance. Likewise, material things are needed as an outward expression of the parents' love: simple—not expensive—gifts, parties, even the privilege of having a friend as a guest at a family meal helps to socialize the normally egoistic child and helps him grow into the attitude of sharing and of finding happiness in giving as well as in receiving. It is channels such as these that lead naturally to the development of a strong and truly mature ego, so needed in adult life.

Lastly, the child's life is complicated by the developing sexual instinct. He is forced to deal with physical and psychological sexual tensions that are to him both unknown and frightening. Sexuality, both physical and psychical, does not occur abruptly at puberty, but is a slowly developing biological phenomenon that progresses through normal phases of growth from the time of birth. The infant is acquainted with no one but himself; consequently he investigates various cavities and appendages of his own anatomy, unquestionably with a pleasurable result. However, it is a moot question as to whether these pleasurable sensations are to be interpreted as of a truly sexual sort. Similarly, pleasurable sensations, equivocally sexual in character, are derived from the excretory processes; hence, the young child's interest and delight in these functions. After this period of erotic interest in self, the child's first object of affection is his mother and, simultaneously perhaps,

he becomes jealous of his father with whom he must share his mother's attentions and affections. But when he goes off to school his sensuous interests are diminished, since he finds new and exciting relationships with other children, is introduced to education and challenged by the multiplicity of activities in the early school years. He is in a quiescent period in so far as his sexuality is concerned. With the advent of puberty momentous changes occur in both the body and the mind. Menstruation is now present in the girl and potency in the boy. Strong emotional and physical sexual interest is aroused, but undirected toward members of either sex. The youngster's ignorance and lack of previous experience leave him uncertain as to whether to pursue persons male or female. Because of convention and associations, more likely than not he temporarily elects a person of his own sex and, if a boy, becomes a male hero worshipper and a girl hater, and the reverse, if a girl. He is passing through a transitory homosexual phase from which he shortly evolves into a realization of heterosexual goals and a definitive heterosexual predilection and adjustment. It is to be stressed that each of these phases is normal, natural, and to be expected; it is only when the child does not advance to the next stage of development, progressing emotionally as well as intellectually, that parents need be concerned—not worried, but merely alert to the child's needs.

THE ULTIMATE GOALS OF THE CHILD

What is it that the child is seeking as he experiences the pangs of growing up? What is his prime objective? This his mentors must clearly see even though he does not: the child's ultimate goal is to learn to behave like a mature adult. And what are the behavioristic signs that designate maturity? Of all the characteristics of the adult that could be enumerated, two are easily paramount: objectivity and courage. They go hand in hand and neither can be present without the other. Both are essential, if one is to be a tranquil, mature individual. By objectivity is meant the ability to separate facts from feelings, the ability to function in terms of the object rather than in terms of self, or, stated another way, the ability to direct one's thoughts "towards external things without reference to personal sensations (Webster)." In other words, the mature individual has learned to deal with life apart from his own personality. Courage is closely allied to objectivity, yet it is not quite the same. Courage implies calmness and firmness in the face of discomfort. It indicates that the individual can control himself in the face of adversity. Such a quality has been designated "tension capacity" and marks the individual as one who can "endure for long the tension between his need and final satisfactions." (Kunkel.)[8] These statements are not to be interpreted as meaning that every child and adult must be a self disciplined stoic and ascetic in order to be termed mature. To the contrary, both parent and child should be eager to see that life is lived to its fullest in each period, with the fewest possible legitimate satisfactions postponed to later periods, when they are usually inappropriate and give much less pleasure than they would have given in the suitable phase of the child's development. But, as with all living, a balance must be maintained, an equation between subjectivity and indulgence on the one hand and objectivity and courage on the other. Parents can best help the child attain this balance by cloaking him in proper attitudes.

POINTS OF VIEW THAT CAN HARM OR HELP THE GROWING CHILD

All that has been said previously is only a prologue to and a foundation for an understanding of the more significant parental points of view and their effect on the child. First to be considered is:

Success or development? Which does the parent want for his child? Should he elect success, he immediately puts the youngster under pressure; pressure to win, pressure to be best, pressure to be good. Very occasionally the child has the innate capacity to achieve his parent's perfectionistic ambitions, but only rarely. More than likely he is an average citizen and not a paragon of scholarship, sports, arts, and virtue; hence, he very early begins to acquire feelings of inadequacy, because he is not living up to the expectation of his parent. Unconsciously, and later consciously, he considers himself a failure, and as a result becomes insecure and unsure of him-

self. Thus, strong feelings of inferiority are evolved from which the child may try to escape by any one of a variety of neurotic forms of behavior. The wise parent chooses improvement as the goal for his child. From the start he expects no more of his offspring than is consistent with his years and his ability. It is growth and steady development that he constantly encourages. If son was on the third string scrub team last year and with great effort makes the second string regular team this year, father lets him know that it is a real accomplishment and does not bemoan the fact that son failed to be captain of the varsity. It is this principle that guides the parent in all of his relationships with his child. He is content with the current accomplishment, but consistently helps the child do better. Accordingly, the child feels adequate, competent, and secure. He develops no patterns of escapism, because he needs none. He is at all times functioning within his capacity and he knows it.

Indulgence or discipline? This is a second decision that each parent must make. It is much easier to say yes than no and, consequently, many children are the unfortunate recipients of such affirmative guidance, popularly known as spoiling. Nothing is more pitiful than the child who has been overindulged. He unwittingly believes that all things come easily in this world, in fact, that they are almost or quite gratuitous for the asking. It is a rude shock for him to learn later that such is not the case and as a result he becomes filled with anger and resentment that are expressed in many ways. More fortunate is the child who from infancy has known firm yet affectionate discipline. Only thus can he learn self discipline, the key to living as a mature adult. In this connection it is well to remember that discipline and punishment are not synonymous. Discipline means obedience to the rules of the game, while punishment means the penalty imposed for infraction of the rules. Unswerving, consistent, friendly discipline is always in order, while punishment should be confined to emergencies. Ideal discipline is best administered by the example of the parent and only occasionally by the spoken word. It is based on the careful planning of a daily routine for the child, careful supervision of the routine and careful evaluation of infractions of the routine. Punishment should be used sparingly and thoughtfully and never as a retaliative measure. When punishment is essential, as should only occasionally be necessary, its administration should always be followed somewhat later by an obvious expression of affection by the parent. Should a child's serious misdemeanor require that very rare spanking, he should not be promptly hustled off to bed but rather, later in the evening, be given a few extra hugs or kisses or a favorite bar of candy. In this way his tendency to consider punishment as synonymous with lack of affection is banished.

Domination or independence? No one likes to be bossed—a child no more so than an adult. But, unfortunately, since a youngster is physically small and, in addition, must face many problems to which he does not know the answers, he is in a vulnerable position. Accordingly, he is apt to be subjected to a continual torrent of do's and don't's. His anger thus aroused is expressed in open rebellion or complete retreat. Hence, we have either the garrulous behavior problem or the timid, submissive, scared rabbit. Is it not wiser to help the child achieve his own independence? Can he not he helped to his own (not his parents') decisions? Surely it is a more fruitful course, because ultimately he must stand or fall on his own (not his parents') merits. Let the child decide for himself—then back him up to make his decisions work out. This breeds confidence and self esteem.

Identification or individualism raises a thought that you may not have considered but which is of prime import to your child. Identification is a mental process by which one unconsciously puts himself in another's place. It is the mechanism by which a parent may unknowingly transfer his personal likes and dislikes, ambitions and frustrations, anxieties and satisfactions to his offspring without regard for the youngster's own tastes, interests and abilities. Obviously, such a subtle and potent force can play havoc as, for example, when the athletically unsuccessful father forces his son into sports in order to satisfy his own frustrated ambitions, or when the educationally underprivileged mother insists upon her mentally dull daughter going to college for a like reason. Is it not better

that the real talents, the real needs and the real capacities of the child be considered so that he be treated as an individual? Because it is as an individual and not as a facsimile of the parent that he must make his way in the world.

Prudishness or frankness is sometimes a difficult problem for the parent to solve. Personal inhibitions and repressions frequently make the father or the mother unwilling to help the child in his anxious pursuit of the truth. It is to be remembered that curiosity is one of the important elements of intelligence and as a result the intelligent child seeks facts. The prudish parent turns aside intimate queries and purposely or unwittingly creates feelings of guilt and shame in the child's mind by leading him to believe that his queries in regard to sex are "dirty" or naughty, or in some way unnice. It is far better to answer the child's questions frankly and in terms he can understand—and then wait for the next question which may not be forthcoming for months or years. Truthfulness given in quantities that the youngster can assimilate at his age and at his stage of development—and no more at any one time than he can comprehend and digest—is the great antidote for fear and ignorance and is by far the best type of sex education. I repeat, questions in regard to sex should be answered briefly and frankly whenever and wherever they arise. That is the ideal type of sex education.

Antagonism and rejection or affection and security? Which will we give our children? Clearly, it is our choice and not the child's. Even an infant rather quickly learns when he is not wanted and becomes unhappy. The parent's excuse may be that he does not have time, that other children require attention or that he did not intend to be neglectful. But more likely than not the motivating force is selfishness and the desire to use his time for his own selfish ends. The thoughtful parent sees to it that his child gets an abundance of attention and affection. No one has to tell such a child that he is loved and wanted; he knows it. Nothing contributes more to the feeling of security than such overt expressions. And the feeling of security is the most essential emotional requirement of all children. Without it loneliness occurs, and no child should be made to feel alone. He must always realize that there is a steadfast, understanding, and sympathetic parent at his side: a parent who guides with affectionate discipline and not with harsh punishment or weak indulgence, a parent who helps him toward independence and does not dominate, and a parent who never rejects but who gives him affection and a sense of security at all times.

Such a consistently friendly and encouraging emotional climate is essential for the child's abundant and stable growth. Children should live always with the sense that they are loved, wanted and trusted; that parents believe in them, know of their trials, temptations and failures, yet also see the times when they have demonstrated self control, have overcome some difficulty or have acted generously with a playmate. This, in effect, is true parental understanding and affection. Words do not create this atmosphere; because, as always, actions speak louder than words. And wise parental actions based on wise parental attitudes are the child's major guideposts to the satisfying life of an emotionally mature adult.

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* * *

So we have reprinted Dr. DuBois' down to earth conception of "parent guidance." It includes all of the essential authoritative information succinctly presented so that all parents may obtain a way of creating a wholesome home environment for their children with the least amount of both ocular and mental effort. Those who follow his suggestions will more than likely overcome the corrupt influence of the ludicrous as well as the shocking antics of many of the "heroes and heroines" of the cinema world both on and off the screen. They likewise will be enabled better to prepare the impressionable little minds to meet the stark and sinister realities of a jittery world which few normal honest adults can wholly comprehend.

At no time in the recorded history of the world has the obligation of *helping the child grow up* been greater.

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Terramycin

A new actinomycete, *Streptomyces rimosus*, has been discovered and isolated from the "good earth" and has been so named because of the cracked appearance of the growth on the surface of an agar medium. When the organism was grown on plates containing nutrient agar and when a variety of bacteria, including certain of the gram-negative enteric organisms, aerobic spore-formers and gram-positive cocci, were streaked across these plates, growth of the test organisms was inhibited in the vicinity of the colony of the actinomycete. Thus again this technic gave a strong lead that this organism caused destruction to the test organisms just as Fleming had observed in the laboratory of St. Mary's Hospital in London with his mold. This mold, which everyone now knows was finally identified as *Penicillium notatum*, gave the world penicillin as well as a simple laboratory procedure which has made it possible to isolate a constantly increasing number of antibiotics.

Terramycin comes from the Research Laboratories of Charles Pfizer and Company, Inc., of Brooklyn where it was developed in their research laboratories by a group of 11 investigators.[1] It is described as being amphoteric and forms crystalline hydrochloride and sodium salts. Crystalline terramycin is soluble in methanol, ethanol, acetone and propylene glycol, in water to the extent of 0.25 mg. per ml. at 25° C. It is insoluble in ether and petroleum ether. Terramycin is stable over long periods in aqueous solutions at a *p*H 2 to 5, at room temperature. It crystallizes in several forms, depending upon the procedure used. One of these forms consists of thick hexagonal plates.

The activity in vitro of crystalline terramycin hydrochloride against a variety of microorganisms has forecast its usefulness as a therapeutic agent. A table lists 14 in which 100 per cent inhibition was obtained in varying amounts used. Conspicuous in this list are staphylococcus, typhoid, paratyphoid and paradysentery organisms. It resembles aureomycin and chloramphenicol, in that it is active in vitro and in vivo and displays marked chemotherapeutic activity against experimental infections in mice due to *Streptococcus hemolyticus, Diplococcus pneumoniae, Klebsiella pneumoniae, Salmonella typhosa* and others. It is effective by both the oral and parenteral routes of administration. Preliminary studies suggest that terramycin has definite antirickettsial activity in chick embryo according to data obtained by Dr. John C. Snyder of the Harvard School of Public Health, which the original authors cite.

A supply of terramycin was made available by the Pfizer Research Laboratories to the Mayo Clinic and a report on a very extensive investigation of some pharmacologic and clinical observations has just appeared.[2] These came from Dr. Wallace E. Herrell, of the Division of Medicine, who has long been recognized as an authority on antibiotics. Associated with him were Dr. Heilman of the Section of Bacteriology and Dr. Wellman and Dr. Bartholomew of the Division of Medicine.

Included in the pharmacologic studies, the method of assay for the determination of the terramycin content of various body fluids was the same method which they had previously described for the determination of aureomycin. The only difference being that terramycin hydrochloride was used in aureomycin hydrochloride as a

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standard. The technic of this test is described in detail in their report.

For the purpose of determining the serum content of terramycin after oral administration, the Mayo group gave single as well as multiple doses of 1 Gm. of terramycin hydrochloride to a number of patients. Single doses were usually given at a time when the stomach was empty. As much as 3 Gm. were given to a few patients. It appears to be readily absorbed and, like aureomycin, it is detectable in the serum a long time after a single oral dose. Complete disappearance of terramycin activity from the serum occurs sometime around 24 to 26 hours after a single dose, although on occasion a detectable amount still may be present at this time. The concentration in the serum, however, begins to diminish six hours or more after a single dose. So the practice of giving multiple doses every six hours was adopted.

Unlike aureomycin, terramycin appears to be fairly stable in the presence of serum. Several specimens of serum were assayed and left under ordinary refrigeration for 24 hours and the assay was repeated. The same amount of terramycin was found as had been found on the previous day. In the case of aureomycin it was necessary immediately to freeze the serum because it was unstable even under ordinary refrigeration.

Up to the time of their report, the Mayo group found that the only satisfactory method of administration of terramycin has been by the oral route. Preparations suitable for intravenous administration are under investigation. For reasons which were clearly apparent in studies on absorption and diffusion, a policy of administering the material every six hours by the oral route was adopted. It appears that 1 to 1.25 Gm. (4 to 5 capsules or tablets) is an adequate and effective therapeutic dose. This roughly represents 4 to 5 Gm. per day for the average adult, and is equivalent to a total daily dose of 50 mg. per Kg. of body weight.

The only untoward reaction encountered in the series at the Mayo Clinic to date of report following oral administration of terramycin is gastrointestinal irritation manifested by nausea and, on occasion vomiting. However, it is contended that the incidence of nausea and vomiting with terramycin is definitely less than with aureomycin. The Mayo group report that the matter of nausea and vomiting, however, has been almost completely controlled by giving the terramycin in milk. The patient simply swallows 1 capsule at a time with cold milk rather than water. Milk does not interfere with the absorption of terramycin, as evidenced by certain studies on serum content which were carried out on patients receiving the drug with milk.

Unlike aureomycin, terramycin does not appear to diffuse well into the cerebrospinal fluid when therapeutically effective blood serum levels are maintained. It does, however, readily pass through the placenta and is available in the fetal circulation. When therapeutically effective amounts are present in the blood serum, diffusion into the pleural fluid occurs. Terramycin appears to be concentrated in the hepatic system and to be excreted in the bile. Patients receiving it excrete fairly large amounts of it in the urine. A great deal of terramycin administered by the oral route is not absorbed but is excreted in the feces. This high concentration of the drug in the feces results in remarkable alteration in bacterial flora of the intestinal tract.

Preliminary clinical trials with terramycin are encouraging. Included among the conditions which have responded in a satisfactory manner are pneumonia, acute follicular tonsillitis and septic sore throat. Urinary tract infections caused by susceptible organisms have likewise responded. In 1 case of *Escherichia coli* infection the results were especially satisfactory. The organism was slightly more sensitive to terramycin than to other antibiotic agents. One patient, critically ill with septicemia due to Bacteroides, made a complete recovery on treatment with terramycin. Another patient with severe erythema multiforme appeared to improve on it. No improvement was noted after the use of terramycin in a patient with herpes zoster.

So far the clinical trials at the Mayo Clinic are only preliminary, but it would appear that in terramycin an additional antibiotic which has proved effective in certain infectious diseases has been obtained. Further clinical results will be watched with interest.

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